PREDICTORS AND HEALTH IMPACT OF EXERCISE CAPACITY IN MULTIPLE SCLEROSIS

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ABSTRACT

Multiple Sclerosis (MS) is a chronic disease with an unpredictable course that impacts significantly on physical performance. Exercise or fitness has become an essential part of management and health promotion for persons with MS. The gold standard measure of exercise capacity (VO_{2peak}) is the maximal exercise test, a graded test that involves an increase in workload until exhaustion is reached. Although this test is the most accurate measure of exercise capacity, it is not clinically useful. Therefore, the main objective of this cross-sectional study is to estimate the extent to which exercise capacity can be predicted by sub-maximal tests in persons with MS. By using data from several functional sub-maximal tests, a regression equation was formulated to estimate the exercise capacity of persons with MS. The results indicated that the modified Canadian Aerobic Fitness Test (mCAFT), grip strength and body weight explained 74% of the variability in VO_{2peak}.

Furthermore, MS literature has shown that health-related quality of life (HRQL) is greatly reduced in MS, as it impacts health perception and capacity to perform daily activities. Therefore, improving HRQL has become an important goal of all health care interventions. It is essential to evaluate and understand patients' own perceptions of the impact of symptoms on their overall health status and their well-being. Thus, the objective of the second manuscript was to estimate the extent to which physical capacity predicts perceived health status in persons with MS. Using multiple linear regression the following variables: sex, vitality, pain, smoking status, walking capacity, social functioning and cognition emerged as significant predictors of the outcome explaining approximately 50% of perceived health status. Significant interaction terms between sex and pain, as well as between sex and vitality were found, indicating that the contributions to perceived health status appear to be different for men and women.

ABRÉGÉ

La sclérose en plaques (SP) est une maladie chronique avec un parcours imprévisible ayant un impact significatif sur la performance physique. L'exercice physique est à présent une partie essentielle de la prise en charge et la promotion de la santé pour les personnes atteintes de SP. La mesure la plus élévée de capacité d'exercice est le test d'exercice maximal, étant un test à échelle qui implique une évolution des charges de travail jusqu'à ce que l'exténuation soit atteinte. Malgré que ce test demeure la mesure la plus precise d'évaluation de capacité d'exercice, il n'est cependant pas cliniquement utile. Par consequent, l'objectif principal de cette étude est d'estimer l'étendue à laquelle la capacité d'exercice peut être predite et ce avec un test sub-maximal sur une personne atteinte de SP. En utililsant l'information puisée de multiple test sub-maximal fonctionnel, une équation régressive peut être formulée pour estimer la capacité d'exercice du patient atteint de SP. Les résultats indiquent que les tests d'aptitude aérobique canadien modifié et de force de préhension ainsi que la masse corporelle explique 74% de la variation du $VO_{2\ peak}$.

D'autant plus, le littérature sur la SP a démontrée que la qualité de vie relative à la santé (QVRS) est immensement réduite dû à la SP car cela a un impact direct sur la perception de la santé et la capacité de performer des activités quotidiennes. Donc, l'amelioration de la QVRS est devenue un but primordial dans toutes les interventions relatives aux soins de santé. Il est essentiel d'evaluer et comprendre comment le patient perçoit l'impact des symptomes sur son statut de santé général et son bien-être. Ainsi, l'objectif du second manuscrit est d'estimer l'étendue à laquelle la capacité d'exercice prédit la perception du statut de santé chez une personne atteinte de SP. L'utilisation de multiples variables de regression linéaire tel que: le sexe, la vitalité, la douleur, la consommation de tabac, la capacité de marche, la fonctionnalité au sein de la société et la cognition permettent l'émergence de prédicteurs significatifs du résultat. Ceci expliquant approximativement 50% du bilan de santé perçu. Les termes d'interactions entre le sexe et la douleur ainsi qu'entre le sexe et la vitalité indiquent que les facteurs contributifs de la perception du bilan de santé diffèrent entre l'homme et la femme.

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PREFACE

Author's contributions

Prior to the completion of this manuscript-based thesis, several important steps were undertaken. At first, the thesis protocol was prepared by Ayse Kuspinar and approved by the thesis' committee members, Dr. Sara Ahmed and Dr. Ross Andersen, and by the thesis supervisor, Dr. Nancy Mayo. In the second step, a literature review on the topic was conducted, which was followed by data collection. In the third stage, all of the collected data have been carefully examined and critically analyzed. All of these tasks have been carried out by Ayse Kuspinar under the meticulous supervision of Dr. Mayo and support of Dr. Andersen.

Organization of thesis

The primary objective of this thesis is to estimate the extent to which sub-maximal fitness tests predict exercise capacity in persons with multiple sclerosis. The secondary objective is to estimate the extent to which exercise capacity predicts perceived health status in multiple sclerosis. Each objective is independently addressed in two separate manuscripts. These manuscripts will later be submitted to scientific journals for publication. In order to follow the regulations of the Graduate and Postdoctoral Studies (GPS), additional chapters have been incorporated in this thesis. As requested by the GPS, a literature review and conclusion independent of the manuscripts have been included. We must admit that duplications are inevitable in this thesis.

Chapter 1 provides an introduction to multiple sclerosis (MS), including information regarding its aetiology, symptoms, epidemiological features and management (both rehabilitative and medical).

Chapter 2 is a literature review on the impact of MS on muscle strength and walking capacity, two common symptoms or consequences associated with the disease course. Both walking capacity and muscle strength have been measured and evaluated in this thesis.

Chapter 3 is a structured literature review of peak aerobic capacity (VO_{2peak}) in MS. A comprehensive literature search with MEDLINE, CINAHL, and Sport Discuss has been carried out, and findings have been systematically analyzed with tables and graphs.

Chapter 4 presents a literature review on the physical fitness measures that were administered in this thesis. The major characteristics and psychometric properties of the measures are presented in this chapter.

Chapter 5 is an introductory chapter to the first manuscript where the rationale objectives of the study are clearly outlined.

Chapter 6 consists of the first manuscript. The study's objective is to estimate the extent to which exercise capacity can be predicted by sub-maximal tests in persons with MS. Findings are presented in tables and references are included at the end of the text.

Chapter 7 links the first manuscript with the proposed objectives of the second manuscript. It explains the rationale behind the second manuscript and its connection to the first manuscript.

Chapter 8 is divided into two sections. The first one is a literature review on health-related quality of life and perceived health status, as these two concepts are an integral part of the second manuscript. The second section consists of the second manuscript on estimating the extent to which exercise capacity predicts perceived health status in multiple sclerosis. It comprises the text, figures, tables and references.

Chapter 9 is a summary of the findings and conclusions of the two manuscripts. The appendices include additional information pertaining to the thesis that was not presented in the manuscripts.

CHAPTER 1

An Overview of Multiple Sclerosis

1.1 Multiple Sclerosis

Multiple sclerosis (MS) is an unpredictable, inflammatory, demyelinating disease of the central nervous system (CNS).[1] The prevalence rate in Canada is one of the highest in the world at 240 per 100,000.[2] MS is the leading cause of neurological disability in young adults,[3] affecting two to four times as many women as men.[4] The patho-physiology involves damage to the nervous system by the body's own immune system.[3] Cells attack myelin sheath and underlying fibres, leading to disruption of signal transmission from the brain to the body.[5]

1.2 Aetiology

The aetiology of MS is unknown, however, there is evidence that both genetic and environmental factors are involved in triggering the disease.[6, 7] Individuals with a parent or sibling who has already been affected with MS have 15% more chance of developing it than the general population.[8] Also, among identical twins, the concordance rate between fraternal twins and identical twins vary considerably, where the rates are 5% and 31% respectively.[7] There is, moreover, some evidence indicating the association of MS with viral infection and some other evidence implicating Vitamin D exposure as rates are higher in regions further away from the equator.[8]

1.3 Course of MS

The course of MS is difficult to predict. In 1996 the United States National Multiple Sclerosis Society confirmed that four main types of MS are generally recognized.[9] The most common form is relapsing-remitting MS (RRMS), characterized by acute attacks followed by full or partial recovery. Fifty percent of patients with RRMS develop secondary progressive MS (SPMS), described by a steady increase in disability with or without acute relapses. Primary progressive MS (PPMS) is distinguished by disease progression from onset and represents approximately 10% of MS patients. The least common known is progressive relapsing MS (PRMS) which is characterized by constant progression of disease from onset with superimposed relapses (Figures 1 to 4).[9, 10]

1.4 Measuring Disease Severity in MS

The most widely used and universally accepted outcome measure of disease severity and progression in MS is The Expanded Disability Status Scale (EDSS).[11] It is a classification scheme extending from 0 (normal neurological examination) to 10 (death due to MS). Scores 1.0 to 3.5 of the EDSS are scored using the Functional Systems (FS) component of the scale. The FS consists of the eight major systems of the central nervous system (CNS), that are pyramidal, cerebellar, brainstem, mental, spasticity, sensory, visual, and bowel and bladder. Scores 4.0 to 9.5 are scored primarily by the ability to ambulate or mobilize. EDSS score of 6 and 6.5 refer to people who require an assistive device for ambulation, and scores 7.0 or greater consist of persons with severe disability, such as those requiring a wheelchair. It is administered by a neurologist and takes approximately 10 to 20 minutes to administer.[11]

There are several advantages and disadvantages associated with the EDSS. It is a widely used scale that enables communication among neurologists and health care professionals through quantifiable methods.[11] It has proven moderate to high concurrent validity against measures of physical function. However, there are also disadvantages associated with this measure. A major limitation is that it lacks sensitivity and reliability. Although some studies have reported high inter-rater reliability ($r = 0.93$), they defined reliability as a difference of ≤ 1.5 points.[11] Therefore, these findings cannot be completely trusted. Most studies have reported low inter-rater agreement. For example, Francis and colleagues reported that observer error accounted for 17% of the variation observed between the EDSS scores. The observer error was even greater within the FS component of the scale, where it accounted for 12% to 55% of the variation observed between scores. In other words, the difference in scoring among the three evaluators ranged from 0 to 4.0 points.[11, 12] However, despite these limitations, the EDSS is still the most widely used and accepted measure of disease severity in clinical practice and research.[11]

1.5 Symptoms of MS

RRMS, mentioned above, is found in approximately 85% of patients, affecting women more than men. The early symptoms include unilateral optic neuritis, diplopia, reduced limb strength, altered sensation, and changes in proprioception, as well as bowel and bladder dysfunctions.[7, 8, 13] One must keep in mind that these symptoms usually appear in the early stages of MS. As such, one can eventually develop other symptoms such as changes in speech, cognition, pain, and sexual function.[7]

On the other hand, PPMS usually affects men more than women. The first symptom is usually progressive weakness of one or both lower limbs.[8] As mentioned earlier, there is no attack or remission, but rather a gradual worsening of symptoms. For instance, quadriparesis, reduced cognitive function, impairments in vision, problems with bowel, bladder and sexual function may eventually develop in patients.[7]

A most common symptom in all 4 types of MS is fatigue, which occurs in more than 75% of patients.[14] Fatigue presents itself either physically, mentally or both. Although there are several hypotheses that have been proposed, and studies that have been conducted by researchers, the pathogenesis of fatigue is still unknown.[14] Nevertheless, as has been shown in those studies, it is associated with psychological distress,[15] elevated negative affect, and a sense of loss of control.[14]

1.6 Epidemiologic Features of MS

Epidemiology is defined as "the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to control of health problems."[16] Prevalence and incidence rates are the two commonly used epidemiological measures of a disease occurrence. Incidence is defined as the number of *new* cases of a disease during a given period in a specified population.[16] Prevalence is defined as the number of events in a given population at a designated time.[16] In other words, prevalence is defined by the number of people affected by MS in a population on a given occasion or time.[17] It is the product of incidence and disease duration.[17] Since MS is a disease of long duration with a life expectancy slightly shorter than the general population, the variability in prevalence can be used as a proxy for the variability in incidence.

Over 400 articles have so far appeared in print on the prevalence of MS around the world.[18] The task of comparing prevalence rates between countries can often be challenging, due to differences in age, ethnic origin, and size of the populations involved.[18] Furthermore, differences in accessibility and reliability of medical care, advancements in research and awareness of the disease may vary from one country to another.[18] In spite of these challenges, studying and being aware of the prevalence (incidence) rates of MS around the world is an essential factor in understanding its aetiology.

Some researchers have proposed that distance from the equator may have an association with the onset of MS. For example, countries that are further away from the equator, such as Canada, the United States, and the United Kingdom have the highest prevalence rates. Variations in rates within different regions of a country can also be found. For instance, in Canada, the increase in the occurrence of MS varies from east to west. In Newfoundland the rates are 100 per 100,000 whereas it is 248 per 100,000 in Saskatoon. Similarly, in the United States, cities closer to the equator, such as Los Angeles, have lower prevalence rates at about 22 per 100,000, whereas in Olmsted County situated in the north, rates were found to be 160. The highest frequency of MS in Europe and perhaps in the whole world is found in Scotland at 187 per 100,000. In countries, such as India and Japan, frequencies are reported to be as low as 1 to 4 per 100, 000.[18] The fact that the frequency is extremely low in Japan raises the question of whether prevalence rates are truly associated with distance from the equator. If this is in fact true, then Japan should have prevalence rates similar to Great Britain.[8]

Additionally, some researchers have suggested that race may have an effect on prevalence, since MS appears to occur more among the white population. For example, in South Africa, MS is almost absent in the black population but present in the white population. However, in the United States, the rates of MS are similar between the two races, which once again supports the hypothesis that environment may play a critical role in the occurrence of this disease.[8]

1.7 Medical Treatment

In 1993, a new immunomudulating agent was approved by the U.S. Food and Drug Administration (FDA) called interferon beta-1b (Betaseron) for RRMS. Shortly after, interferon beta-1a (Avonex, Rebif) and glatiramer acetate (Copaxone) were also approved.[19] This group of immunosuppressive drugs are referred to as Disease Modifying Agents (DMA) and have played a critical role in the advancement of MS management. Clinical trials demonstrate that these therapeutic agents decrease the frequency of relapses and slow functional decline in RRMS.[20-22] However, the effects of these medications on progressive forms of the disease (PPMS and SPMS) are not so promising as they are expected to be. Some studies have demonstrated that certain DMA may have an effect on reducing the rate of relapses in SPMS as well, however, no benefits of them on PPMS have been found.[7]

During the occurrence of an acute relapse, patients are usually treated with intravenous methylprednisone for three to five days or with oral prednisone taper for two to three weeks. These forms of intervention are solely used for reducing severity of relapses but have no effect in altering disease progression.[19]

1.8 Rehabilitation

Impairments associated with the disease can lead to a gradual deterioration of functioning in daily life, hence, rehabilitation remains a major strategy in maintaining and improving functional status.[23, 24] Optimizing level of activity and participation through exercise is an essential part of management for persons with MS.

Many of the symptoms associated with MS can be improved with exercise which in turn slows down functional deterioration. Exercise helps improve muscle strength[23], balance[25], fatigue[26], and endurance[23]. It also provides sense of mastery and this, along with symptom alleviation, impacts favourably on quality of life.[27]

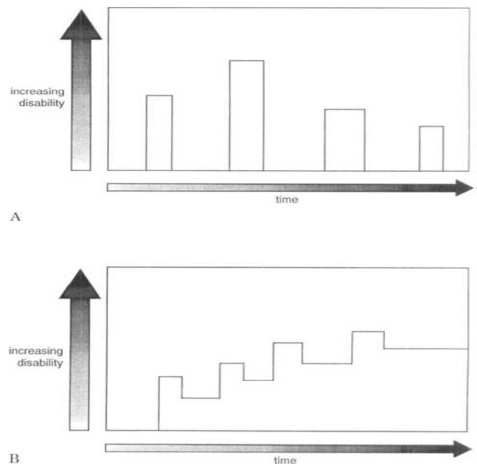
Kraft et al published a review on the current existing research on rehabilitation in MS and provided a list of recommendations for future research.[28] He stated that evidence-based practice in MS has evolved over the past several decades, where MS has transitioned from being a "disease of ambulation" to one that is complex, involving the interaction of numerous systems in the body. Thus he emphasized that rehabilitation needs to focus beyond ambulation and target more complex problems such as fatigue, pain and cognition, participation and employment.[28] Similarly, Mayo stated in an editorial that as MS is a condition solely affecting the brain, future intervention strategies need to target the brain rather than the peripheral system to improve function.[29]

1.9 The New MS

In her article "*Setting the agenda for multiple sclerosis rehabilitation research*", Mayo has suggested that the persons who were diagnosed with MS over the last decade will probably not have the same disease course as the people who had been diagnosed decades ago.[29] Prior to 1995, intervention was mainly based on symptomatic treatment, such as steroids for relapses and baclofen for spasticity. However, in the past decade new disease modifying drugs, such as interferon Beta and glatiramer acetate, have been developed.[19] These are shown to be effective in modifying the course of MS. Furthermore, during the last 10 to 15 years, magnetic resonance imaging (MRI) has played a pivotal role in early diagnosis of the disease.[30] Prior to this, detection was simply based on the natural history of disability signs and symptoms. For this reason, Mayo proposed the title *The New*

MS for persons diagnosed in the era of neuro-imaging and advanced therapeutic treatments. People with the *New MS* are diagnosed earlier with milder forms of the disease that do not follow the same course as the "Old MS". For example, in the United States in the 1980s the average time from symptom onset to diagnosis was 7 years, whereas in the 2000s this gap closed to 1 year. If we evaluate the situation only from lead-time, we will observe a reduction in the severity of MS over time.[31] Thus, Mayo suggested that the recognition of this era is an important methodological requirement in designing studies in this field.

In this chapter we have tried to provide an overview of multiple sclerosis; in the next chapter we shall evaluate two common physical effects of MS; reduced strength and walking capacity.



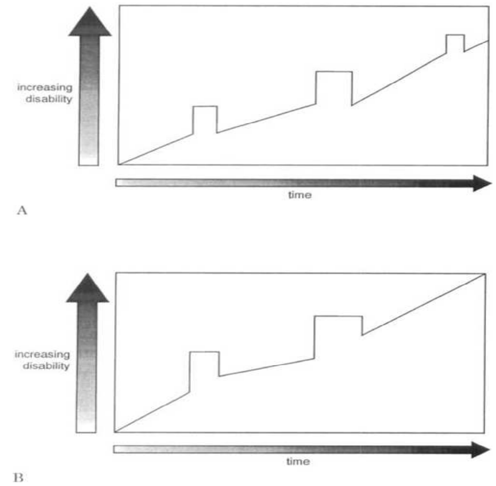
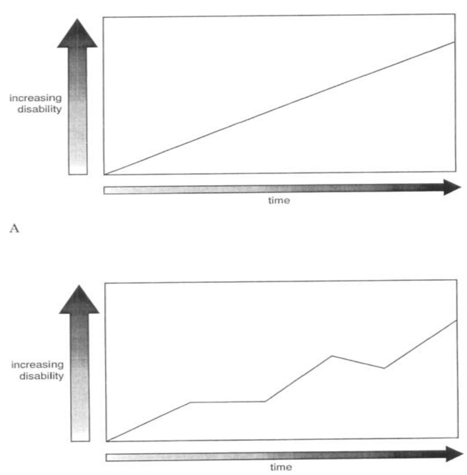


Figure 1. Relapsing Remitting MS is characterized by acute attacks followed by full recovery (A) or partial recovery (B



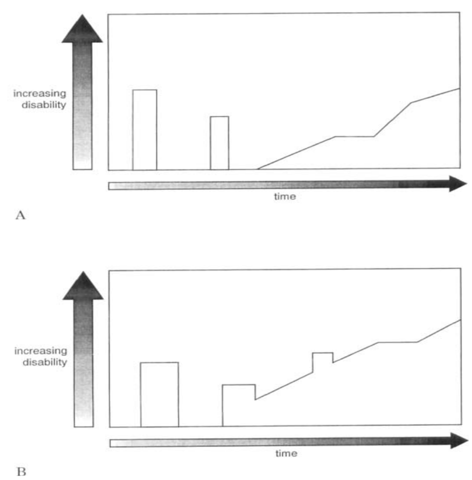
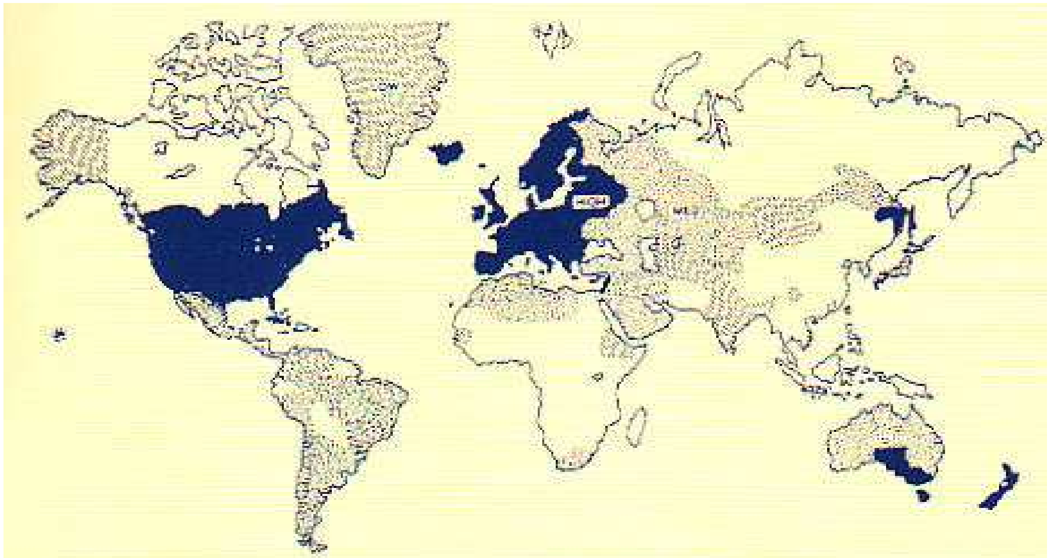


Figure 3. Primary Progressive MS is characterized by disease progression from onset without plateaus or remissions (A) or with occasional plateaus with temporary minor improvements.

Figure 4. Secondary Progressive MS begins with an initial relapsing remitting course followed by progression of variable rate (A) that may include occasional relapses (B).

Taken from: Lublin and Reingold "Defining the clinical course of multiple sclerosis: results of an international survey." *Neurology* 1996; 46:907-911.

Figure 5



Worldwide distribution of MS as of 2002 with high (prevalence 30+ per 100,000; solid), medium (prevalence 5-29; dotted), and low (prevalence 0-4; dashed) regions defined. Blank areas are regions without data, or people.

Taken from: Multiple Sclerosis: Diagnosis, Management, and Rehabilitation. Chapter 3 by John F. Kurtzke and Mitchell T. Wallin.

CHAPTER 2

2.1 The Impact of MS on Muscle Strength

Skeletal muscle strength is defined as "the maximal force a muscle or muscle group can produce at a specified velocity".[32] It consists of four components: force, velocity, movement pattern, and body position.[33] Reduced muscle strength is found in more than 50% of MS patients and is believed to be caused by the changes in the peripheral and central neuromuscular systems.[23, 34] It is an important symptom, as it can have a significant impact on an individual's ability to walk, perform daily activities, and work. Weakness in MS patients may occur in many different forms, such as hemiparesis, paraparesis, or monoparesis.

Several studies have evaluated the possible causes of the strength deficits found in MS. According to the views of some researchers, such strength deficits happen because of increases in central motor conduction time as a result of demyelination in the central nervous system.[35] Other researchers have shown that it may be due to decreased activation and decreased firing rate of motor units in the affected muscle.[23]

De Haan and colleagues have studied the maximal voluntary contractile (MVC) force of the quadriceps muscle in MS patients compared to healthy controls. Seventeen MS patients with a mean age of 41.7±7.8 years and Expanded Disability Status Score (EDSS) ranging between 2 and 6 (mean 3.8) were compared to 16 age matched sedentary healthy individuals.[36] Their findings have indicated that MS patients have significantly lower (31.2%, $p<0.05$) MVC force than healthy individuals. Also, MS patients were only able to generate 75±22% of their maximum force generating capacity, whereas the control subjects were able to exert 94±6% of their maximum muscle capacity. In other words, percentage of maximal force that can be produced during voluntary effort is significantly reduced in MS patients.[36]

The same group of researchers conducted another study with the same group of patients to evaluate upper limb strength in MS patients compared to healthy controls.[38] The adductor pollicis muscle that functions to adduct the thumb was assessed. MVC was significantly ($p=0.02$) less for MS patients (78.1±15.9N) than the control subjects (94.6±22.5N). However, unlike the lower limb, there were no differences found in maximum force generating capacity between the two groups. The percentage of maximal muscle force that was recruited during voluntary contraction was 95.5±3.9% for MS patients and 98.2±2.0% for the control subjects ($p=0.10$). Besides, no significant differences were found between the groups in the contractile characteristics of the adductor pollicis, rates of force development, and maximal power production. As suggested by the authors of the study, these findings may imply that upper limb strength is less affected than lower limb strength in MS patients with mild to moderate disability.[38]

These strength deficits are not only due to central changes, but also because of morphological changes in muscles.[23] Some studies have found that patients with MS have reduced muscle mass.[35, 39] Because muscle mass is an important determinant of muscle strength, several studies have examined muscle size in this disease group. Kent Braun et al. measured cross-sectional area of the tibialis anterior muscle in nine MS patients (median EDSS score 4, range 2 to 6) and eight sedentary healthy controls. The two groups were matched on age, height, and weight. With the use of magnetic resonance imaging (MRI), they demonstrated that there is a 30% reduction ($p = 0.01$) in fat free mass in the anterior compartment of the lower leg in MS patients compared to healthy subjects. This indicates that significant atrophy or muscle loss may be found in persons with MS. However, other studies could not reach this finding.[40, 41] For example, Ng et al evaluated cross-sectional area in a study with a larger sample size of 18 MS patients and 18 age-matched sedentary controls.[42] For the MS group, 12 patients ambulated without assistance, 4 used a cane, and 2 used a walker or wheelchair for mobility. Contrary to the findings by Kent-Braun, there were no differences ($p = 0.11$) in the cross-sectional area of ankle dorsiflexor muscle between MS patients (8.5±0.5cm^2) and sedentary controls (9.8±0.6cm^2).[42]

There have also been reports that MS patients undergo changes in the muscle fibre area of their lower limbs. Kent-Braun found a difference of 26% in muscle fibre area ($p<0.04$) between MS patients (3,694 ± 320µm^2) and healthy controls (4,971 ± 464µm^2).[39] Garner et al also measured the cross-sectional area of one of the quadriceps muscle (vastus lateralis) in 6 MS patients with moderate disability (EDSS score of 4.75 ± 0.28). Their comparison group was six age and gender matched sedentary subjects without MS. The authors observed significant differences ($p<0.05$) in cross-sectional area between MS patients (5,672 ± 175µm^2) and controls (6,153 ± 165µm^2).[35] On the other hand, Carroll et al. did not see any dissimilarities in muscle mass in their study.[40] Seven MS patients (EDSS scoring 6, ranging from 2.5 to 6.5) and seven age, weight, and height matched controls were studied. Interestingly, the investigators did not find any differences in muscle mass between the groups ($p>0.7$).[40]

Changes in muscle fibre type composition have also been shown in MS. Generally speaking, there are two types of muscle fibres, slow twitch fibres (Type I) and fast twitch fibres (Type IIa and IIb). Slow twitch muscle fibres generate energy muscle contractions over continuous or prolonged periods of time. Fast twitch muscle fibres, on the other hand are mainly used in generating rapid movements or force.[43] Among people who have become immobilized, hemiplegic, or have sustained a spinal cord injury, we see a reduction in type I fibres and an increase in Type II fibres.[39] Kent-Braun and colleagues studied 9 MS patients with moderate degree of disability (median EDSS 4, range 2 to 6) and age-matched sedentary controls. They have noticed a significantly ($p<0.05$) higher percentage of Type IIa fibres in MS patients (28.2 ± 5.9%) compared to sedentary controls (19.2 ± 1.8%), and as a result suggested that the changes similar to those found in healthy subjects exposed to immobilization can be seen in MS patients, as well. However, other studies that were conducted on muscle fibre type composition could not verify this, but instead they showed that the composition was similar to healthy persons. For example, Carroll et al[40] examined a sample of MS patients with similar levels of disability as the group of patients studied by Kent-Braun[39]. Suprisingly, he did not find significant differences between MS patients and healthy controls in fibre type composition.[39]

In summary, there are both central (neural) and peripheral (morphological) mechanisms that contribute to muscle weakness found in MS.[23, 44] Central mechanisms include conduction block or failure of axons in the central nervous system. Peripheral changes in the skeletal muscle likely occur as a result of reduced physical activity and atrophy.[44] As Dalgas states in his review, impairments found in MS, including muscle weakness, are probably the result of both the disease process *per se* (changes in the CNS) and inactivity secondary to the disease. These impairments in strength can then lead to reduced functional capacity and reduced quality of life.[23] Therefore it is extremely important to reinforce exercise as a rehabilitative strategy, in order to improve disability and the overall health profile of these patients.[23]

2.2 Impact of MS on Functional Walking Capacity

Walk performance is crucial to the severity classification of MS. A measure that is used to determine disease severity in MS is the Expanded Disability Status Scale (EDSS), which is strongly dependent on patients' ability to ambulate. However, when administering this scale, no standard walking test is used. Instead, physicians rely on the patient's self-reported walking distance.

There are several standardized walking tests that have been utilized to evaluate functional capacity in various patient groups including patients with MS. One that is well recognized and that has been repeatedly used in studies is the six-minute walk test (6MWT). It is a simple performance-based test that requires minimal equipment. According to this test, individuals are instructed to walk as far as possible in an empty corridor, in six minutes at their own intensity.[45]

A similar finding noticeable among all studies is that six-minute walk distance (6MWD) is reduced in persons with MS compared to healthy subjects.[46-48] Based on an assessment of 30 MS subjects with moderate disability, Savci and colleagues found that the distance walked by them, was significantly reduced ($p<0.0001$) when compared to healthy control subjects of similar age, height and weight. Subjects with MS ambulated on average 380 metres, whereas the control group ambulated almost double the distance at 618 metres.[46]

Paltamaa et al. measured distance walked in MS subjects in a study whose primary aim was to evaluate the psychometric properties of the 6MWT in 19 subjects with mild to moderate disability and mean age 42 years.[47] They conducted three trials of the test, where the average distance walked and standard deviations were 538 ±167 m, 545 ±159 m, and 555±172 m respectively.[47] Although these values are considerably higher than those reported by Savci et al., they seem still low compared to healthy individuals.

Recently, Goldman et al. evaluated distance ambulated between 40 MS subjects and 20 healthy controls.[48] Both groups were similar in age (mean 41 years), height and weight. When they compared the group of MS patients altogether to the healthy subjects, MS subjects ambulated significantly less ($p<0.0001$) than the control group. The control group walked approximately 620m in six-minutes, whereas the MS group walked about 518m.[48] The authors decided to divide the MS patients into 3 groups according to level of their disabilities and then compare each sub-group to healthy subjects. Level of disability was defined by the Expanded Disability Status Scale (EDSS)[37]. In this study, 15 subjects had mild disability (EDSS 0 to 2.5), 19 had moderate disability (EDSS 3.0-4.0), and 6 had severe disability (EDSS 4.5 to 6.5). Patients in the mild group walked about 603 ±48.5m, almost the same distance as the control group who had walked on average 620 ±49.1m. The moderate and severe disability groups walked 507 ±103m and 389 ±77.7m respectively.[48] The values for the latter two groups were much lower than the control group, indicating that walking capacity may be affected by disability levels.

In summary, distance ambulated during the 6MWT is certainly a practical and useful measure, for it can help identify any limitations in an individual's functional capacity. From the existing literature, we can reasonably reach a conclusion that functional capacity is generally reduced in persons with MS, and to a certain degree, is affected by level of disability.

CHAPTER 3

Exercise capacity in persons with multiple sclerosis: a literature review

Introduction

Over the years physical fitness appears to have been defined in several ways by various organizations in North America. According to the World Health Organization's definition fitness means "the ability to perform muscular work satisfactorily."[49] The American College of Sports Medicine likewise has defined it as "the ability to perform moderate to vigorous levels of physical activity without undue fatigue and the capability of maintaining such ability throughout life."[49]

Fitness is generally divided into two components: one related to health-related fitness and the other related to skill-related fitness (Figure 3.1).[49] The first is comprised of 5 factors: (a) cardio-respiratory endurance, (b) muscular endurance, (c) muscular strength, (d) body composition, and (e) flexibility. The latter consists of agility, balance, coordination, speed, power and reaction time. [49] Although skill-related fitness plays an important role in an athlete's ability to perform during team or competitive sports, it is less important when it comes to improving the overall health of the individual.[49] Health-related fitness, particularly cardio-respiratory fitness, has been more emphasized, since it is associated with mortality and morbidity.

Furthermore, in order to measure the cardio-respiratory fitness of an individual, a maximal exercise test is performed.[50] Such a test is usually carried out on a treadmill or bicycle ergometer which is recognized as the best measure of cardio-respiratory capacity or fitness.[51] It assesses maximum aerobic capacity (VO_{2max}), which is defined as the maximum amount of oxygen that a person can take up, transport, and utilize during exercise.[49] The values extrapolated from this test are typically presented as absolute (L/min) or relative to body weight (ml/kg/min).

In multiple sclerosis (MS), exercise is used as a major rehabilitative strategy to improve cardio-respiratory and muscular function. Therefore, over the years, various studies have employed maximal exercise testing to measure cardio-respiratory fitness in persons with MS. In MS, as is the case with most diseased populations, a true VO_{2max} is difficult if not impossible to obtain. Therefore, the peak aerobic capacity (VO_{2peak}) is recorded instead. As has been generally accepted, people with MS have lower exercise capacities than the general population. This is indeed a grave concern, as physical inactivity is known to increase risks of heart disease, diabetes, and premature death. In fact, studies have found an increased incidence of osteoporosis[52] and death from cardiovascular diseases[53] in persons with MS. As such, the objective of this literature review is to offer a critical summary of the findings and the results that have been reached by the researchers on exercise capacity of persons with MS.

Methods

Search Strategy

A comprehensive literature search using Medline, CINAHL and Sport Discus was carried out for the time period from 2000 to October 2008. Search terms included "exercise, capacity, exercise test, exercise tolerance, oxygen consumption, physical endurance and multiple sclerosis."

Inclusion & Exclusion Criteria

Only empirical work that measured relative VO_{2peak} (ml/kg/min) in MS patients, using leg ergometry, arm-leg ergometry or treadmill, was included for review. Non-English publications, case studies, commentaries, editorials, reviews, conference abstracts, dissertations, and experiments that studied other neurological diseases alongside MS were excluded. From a pool of 212 studies, only 8 studies met inclusion and exclusion criteria, and were included for review.

Data extraction

The total sample size from these 8 studies was 202. Six of these studies used cycle ergometer and 2 used arm-leg ergometer. All of the studies used the Expanded Disability Status Scale (EDSS) to evaluate disease severity. The EDSS is a 10-point scale where a higher score indicates greater disability. EDSS scores of 0 to 4.5 refer to people who are fully ambulatory and yet have some neurological deficits in the following areas: pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral and other. Scores 4.5 to 6.5 refer to people who ambulate with assistance, and scores greater than 6.5 refer to people who are able to take few steps or are wheelchair bound[37]. The study samples included MS patients from the USA, Iceland, Finland, Germany and Italy. Study designs consisted either of clinical trials, single group pre-post design, or cross-sectional observations.

Description of the 8 studies

In 2007, Rampello and colleagues conducted a randomized crossover controlled study to evaluate the effect of an 8-week aerobic training program, compared to usual care, on walking capacity and maximal exercise capacity.[54] Although 19 subjects were initially recruited for the study, only 11 completed it and were included for analyses. These patients had mild to moderate disability (median EDSS of 3.5, range 1 to 4) and were on average 44±6 years old. Exercise capacity (VO_{2peak}) was the primary outcome used and was measured at baseline and post intervention for both groups. For this review, we will only look at the pre-intervention values. The baseline VO_{2peak} values for the aerobic training group was 17.1±7.0 ml/kg/min and 16.8±6.5 ml/kg/min for the usual care group.[54]

Bjarnadottir et al published a randomized controlled study in 2007 to evaluate the effect of aerobic and strength training on physical fitness and quality of life in persons with MS.[55] A total of 16 MS patients completed the study, where 6 were randomized to the intervention group and 10 were randomized to the control group. The entire sample consisted of 11 females and 5 males, with a mean age of 37.4 years and EDSS score of 1.95. All participants underwent a graded bicycle test pre and post intervention. At baseline, the mean VO_{2peak} value in ml/kg/min was 27.3 for the intervention group and 23.4 for the control group. The average oxygen consumption for females was 21ml/kg/min and 33ml/kg/min for males.[55] Unfortunately, no standard deviations for these numbers were provided.

Schulz et al examined the effect of an 8 week aerobic training program on immunological, endocrine and neurotrophic factors as well as coordinative function and quality of life.[56] They measured maximum exercise capacity using a cycle ergometer pre and post intervention. In order for the subjects to be included in the study, they were all required to reach at least 100W during the incremental cycle ergometer testing. A sample of 28 MS patients were randomized into the training group or the control group. The average age for the training group was 39±9 years with and an EDSS score of 2.0±1.4. The values for the control group were similar with a mean age of 40±11 years and EDSS score of 2.5±0.8. VO_{2peak} was used to evaluate any changes of fitness for the two groups at the end of the 8 weeks in comparison to their baseline values. Although several biological parameters were also measured, for the purpose of this review we are only interested in the baseline VO_{2peak} values. The average relative VO_{2peak} was 33.1±7.1 in the training arm, and 28.9±7.8 for the control arm.[56] Although, these values are still low compared to norms, they are slightly higher than the findings of the 2 previous studies. This may be partially influenced by the fact that only the patients who were able to reach at least 100W with a VO_{2peak} test were allowed to participate in the study, and excluded less fit patients.

Maximal oxygen uptake was measured in a study by White and colleagues to evaluate the effects of pre-cooling on fatigue, gait and oxygen consumption.[57] Six patients (3 female and 3 male) were instructed to exercise at 60% of their VO_{2peak} for 30 minutes under non-cooled and pre-cooled conditions. An arm-leg ergometer was used to measure VO_{2peak} in these patients before exposing them to the 2 different experimental situations. Their mean age was 46±7 years and mean EDSS score 3.1±0.9 ranging from 2.0 to 4.5. The average VO_{2peak} recorded was 30.4±8.2 ml/kg/min.[57]

Davis et al examined sweating characteristics in 10 women with MS compared to healthy controls.[58] VO_{2peak} values, along with age, height and weight were used to match each MS participant with a healthy control. The authors matched individuals on their VO_{2peak} values to ensure that any of the observed differences in sweat function between groups was not influenced by aerobic fitness. The average age of the MS patients was 44.7±8 years, and average EDSS score was 5.2 ±1.3, ranging from 3 to 5. The mean VO_{2peak} value was 26.0 ml/kg/min with a standard deviation of 5.9ml/kg/min.[58]

In 2004 Romberg and colleagues conducted a cross-sectional study to estimate the extent to which exercise capacity can be predicted by disease severity and leisure physical activity.[59] A total of 95 MS patients were recruited from an inpatient rehabilitation hospital, of which 61 were women and 34 were men. The average age for women was 43.5±6.6 years with an average EDSS score of 2.2±0.9. For the men it was 44.4±6.8 years and 3.0±1.2, respectively. Out of this sample, one male and two females were unable to complete the cycle ergometer test. The VO_{2peak} value for the men was 27.0±5.2 ml/kg/min and for the women it was 21.7±5.5 ml/kg/min.[59]

In 2006 Prakash and colleagues evaluated cardiorespiratory fitness as a predictor of cortical plasticity in 24 women with multiple sclerosis.[60] Their mean age was 44.71±7.07 and mean EDSS score 2.61±1.76. All participants performed an incremental cycle ergometer test to measure their VO_{2peak}. Results were divided into a low-fit group, whose mean VO_{2peak} was 16.68±2.13 ml/kg/min and a high-fit group, with mean VO_{2peak} 25.41±4.82 ml/kg/min.[60]

In 2008, Morrison et al evaluated perceived exertion in patients with MS, compared to healthy controls, while undergoing a graded maximal exercise test.[61]

A total of 12 MS patients with mild disability (mean EDSS 2.75, range 0 – 3) and average age 38.3±4.9 years were included in the study. The average VO_{2peak} recorded during a graded maximal cycle ergometer test was 22.9±6.2 ml/kg/min for this group of patients.[61]

Results

A total of three randomized clinical trials used a graded exercise test to evaluate the effect of an exercise program. One study used it to match between individuals in 2 groups to ensure that differences found would not be impacted by their cardiorespiratory fitness. Two cross-sectional studies evaluated the relationship between VO_{2peak} and different variables such as disability, physical activity, and neural plasticity. One study evaluated the effects of 2 experimental exposures on aerobic capacity, and another looked at perceived exertion in MS patients, compared to healthy controls, while undergoing a maximal exercise test.

Together, the 8 studies included a total of 202 participants who underwent a graded maximal exercise test. The weighted mean age of the patients was about 40 years, with roughly 70% of them being female. Patients mostly had mild to moderate disability, with a weighted mean EDSS score of approximately 2.7. The criteria for inclusion and exclusion were similar between studies. Usually, subjects who had a relapse in the preceding month or who had cardiovascular or musculoskeletal impairments were excluded.

A forest-plot of the VO_{2peak} findings in these studies is provided in Figure 3.2. The name of the author for each study is presented on the left-hand side column. The mean VO_{2peak} and its confidence interval are on the right-hand column of the plot. The area of each square on the graph is proportional to the studies sample size, and the horizontal lines indicate the width of the 95% confidence intervals. As demonstrated by the forest-plot, findings ranged from 13 ml/kg/min to 37 ml/kg/min. We calculated the weighted mean VO_{2peak} of the sample to have an idea as to where these patients stand in terms of exercise capacity compared to healthy individuals. The weighted VO_{2peak} for the entire sample was about 24 ml/kg/min. When we compare this value of to normal healthy individuals of the same age group, they would be situated at the 10^{th} percentile level.[62]

Discussion

This exceptionally low value found in MS brings forth the question of why this is so. Why is cardiorespiratory fitness considerably lower for persons with MS than the normal population?

First, it is well established that physical activity is considerably reduced in persons with MS when compared to non-diseased persons.[63] In a meta-analysis by Motl and colleagues individuals with MS were found to be significantly less physically active than non-diseased persons. They concluded that the difference in levels of physical activity was great and close to 1SD, but had a zero-order effect when compared to other diseased individuals such as chronic fatigue syndrome. This difference was even greater when measured using an objective measure such as an accelerometer, compared to self-reported measures.[63] The authors of the meta-analysis also suggested that men may be more physically inactive than women, as the former are more likely to be diagnosed with progressive forms of the disease and have higher levels of disability than the latter. [63]

Some researchers have proposed that disability levels may affect exercise capacity.[64] Koseoglu et al examined the association between disability and exercise capacity in 25 individuals with MS. They found statistically significant, moderate correlations ($r = -0.453$) between EDSS and exercise capacity.[64] Romberg and colleagues also examined the association between these two variables on 92 persons with MS. They found a moderate inverse Spearmen's correlation ($r = -0.50$, $p=0.004$) for men, but weak correlations for women (r =

-0.25, p=0.05).[59] These findings imply that disease severity may be an important predictor of exercise capacity in MS for men.

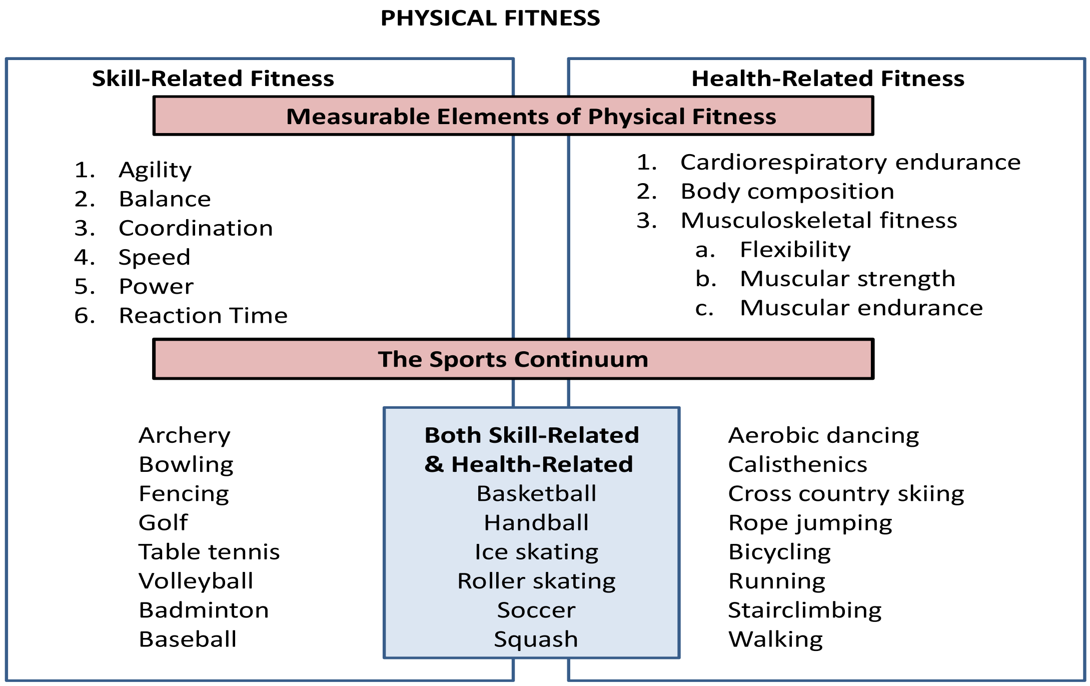
Fatigue is a common disabling symptom that can be found in up to 75% of MS patients. The underlying pathophysiology of MS related fatigue is multifactorial.[65] Primary causes may include changes in immune system activity, changes in the central nervous system, endocrinal abnormalities, as well as changes in neurotransmitter regulations.[65] Of course, fatigue may be also caused by various symptoms associated with MS such as pain, sleep dysfunction, depression and physical deconditioning.[65] Regardless of the cause, fatigue may lead to reduced physical activity, which then can initiate de-conditioning that eventually leads to further increases in fatigue.[54] This vicious cycle may be a possible explanation of the reduced exercise capacity found in persons with MS.

Respiratory muscle weakness is another possible contributing factor to account for the reduced aerobic capacity. Respiratory muscle weakness has been reported to occur not only in patients with severe MS, but also in patients with mild MS.[64, 66] Foglio et al questioned the extent to which respiratory muscle function was related to exercise tolerance in 24 ambulatory MS patients.[67] Not only did they find that respiratory muscle strength was significantly reduced compared to predicted values, but also that there is a significant moderate correlation between respiratory muscle strength and work capacity.[67] Similar results were found by Koseoglu et al.[64]

Some other factors that may attribute to reduced exercise tolerance are cardiovascular autonomic dysfunction[68, 69], increased perceived effort[70], changes in core temperature[57] and lower leg weakness[71].

In conclusion, it appears that persons with MS present with marked reductions in exercise capacity compared to healthy individuals. This may be as a result of the disease process *per se* or as a result of the decreased physical activity levels seen in these patients.[23] Reduced aerobic capacity can have severe consequences on one's overall health, leading to increased risk of cardiovascular diseases, obesity, osteoporosis and early death.[23] Therefore, it is important to address the multi-factorial components associated with poor cardiovascular capacity, through the implementation of exercise interventions and promotion of active lifestyles in this disease group.

Figure 3.1

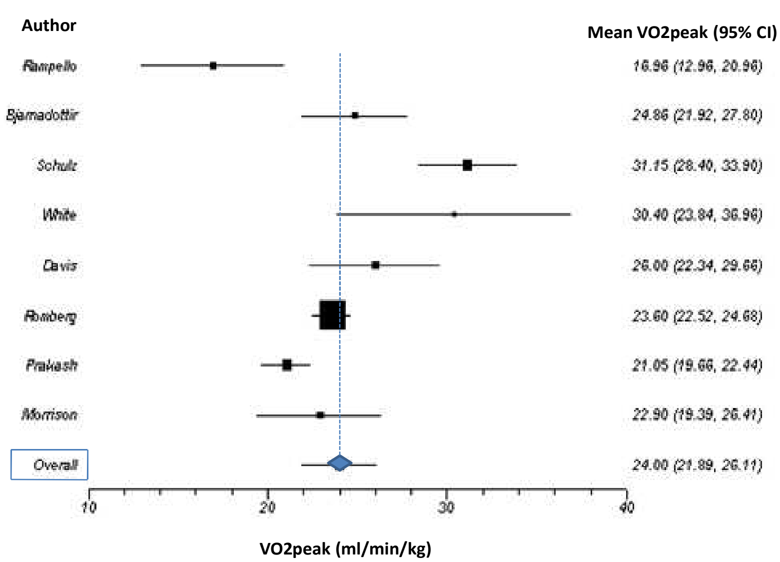


Source: Adapted from David C. Niemen. Exercise Testing and Prescription: A Health Related Approach 6ed.

Table 3.1 Characteristics of study participants

Sample size (n)	202
Weighted Mean EDSS (n=191)	2.7
Weighted mean age, years	40.4
Mode of testing	Cycle ergometer: 6 Arm-leg ergometer: 2 Treadmill: 0
Time since diagnosis, years (n=172)	7.2
Weighted mean VO_{2peak} (ml/kg/min)	24

Figure 3.2 Forest plot of VO_{2peak} (ml/kg/min) in persons with multiple sclerosis



*Standard Deviation for the overall mean is assumed from the study by Romberg as it has the largest sample size

CHAPTER 4

In this chapter, we shall make a review of all the maximal and sub-maximal tests that we have used in the first manuscript. We shall also describe the procedures and the psychometric properties of these fitness tests.

4.1 Maximal Exercise Test

Maximal exercise testing is a graded test that involves an increase in workload until exhaustion is reached. It measures maximum aerobic capacity (VO_{2max}) which is the maximum amount of oxygen that a person can take up, transport, and utilize during maximal exercise testing.[50] In MS and other diseased populations, a true VO_{2max} is difficult to obtain because patients usually cease exercising before a maximal workload is reached. This is due to a variety of reasons such as leg pain or fatigue. Therefore, the peak aerobic capacity (VO_{2peak}) is recorded instead.

There are two well-known modes of exercise testing, one treadmill testing and the other bicycle ergometer testing. Exercise testing using a treadmill is the better method of determining exercise capacity in healthy people, since it yields higher VO_{2max} results.[72] Hermansen and Saltin found 7% greater oxygen uptakes during maximal running compared to cycling.[73] This is because treadmill exercise involves greater muscle mass[73], and less hemodynamic stress on the body[74]. However, for persons with orthopaedic or neurological impairments, maximal treadmill exercise is strongly discouraged.[75] Since persons with MS are likely to have abnormal gait, impaired balance and need of handrail support, this form of testing may not be suitable for them. It may not only cause concerns regarding patient safety, but also yield inaccurate conclusions.[75] For example, a study by Christman et al. demonstrated that continuous use of handrails during treadmill exercise results in significant reductions in oxygen uptake.[76] Because of all of these genuine reasons, this thesis project will employ a cycle ergometer to determine VO_{2peak}. A test as such will be relatively safer and easier to administer, because the subjects will be in a seated position.

4.2 Modified Canadian Aerobic Fitness Test (mCAFT)

The Canadian Aerobic Fitness Test (CAFT) is a multi-stage step-test that assesses sub-maximal aerobic capacity.[94] It was originally designed for use in the home as it is simple to use and inexpensive.[95, 96] Jette et al. developed a multiple linear equation to predict aerobic capacity for healthy individuals from this test.[97] Investigators soon discovered that this formula under-estimated VO_{2max} and thus questioned its reliability and validity.[96] As a result, the protocol and the equation were modified to better estimate VO_{2max}. This new test was given the title, "the modified CAFT (mCAFT)".[96]

Canadian norms for this test have long been established and are still widely used. Although the test was originally designed to allow Canadians to monitor their levels of physical activity at home, over the years it has been employed in industry and clinical studies to define fitness levels and predict VO_{2max}.[98]

Subjects complete all the stages necessary to achieve 85% of their maximum predicted heart rate. Each stage is 3-minutes in duration and progressively more challenging.[94] Oxygen cost, along with the individuals' age and weight, is entered in a standard equation that predicts VO_{2max}.[96]

This test has a high test-retest reliability with an intra-class correlation coefficient of 0.97 for males and 0.98 for females.[99] The Pearson correlation coefficient (r) of predicted VO_{2max} against measured VO_{2max} is 0.88 and the mean square error is 37.0.[95]

4.3 Six-Minute Walk Test (6MWT)

The 6MWT is a simple performance-based test that measures functional exercise capacity.[45] It is usually conducted in a flat enclosed corridor where individuals are instructed to walk as far as possible in six minutes at their own pace. Although they can rest at any time during the test, they are encouraged to resume walking, as soon as they are ready to do so. The number and duration of rests, as well as the total distance ambulated are recorded. Rate of perceived exertion, fatigue, and heart rate are assessed before and immediately after testing. At the same time, standardized instructions are used. [45, 77]

The reliability of the 6MWT has been assessed in persons with MS by Paltamaa and colleagues. The intra-class correlation coefficient (ICC) is 0.96 for test-retest reliability and 0.93 for inter-rater reliability.[47] These findings are similar to other studies that have evaluated the reliability of this test in different groups of populations. In persons with chronic heart and lung disease, test-retest reliability is 0.91.[78] Among individuals with fibromyalgia, the ICC ranges from 0.73 to 0.98,[79, 80] and in healthy elderly individuals this coefficient is between 0.93[81] and 0.95[82]. High ICC values (≥0.90) have also been reported in persons with peripheral arterial disease[83], heart failure[84-86], and end-stage lung disease[87].

Concurrent validity of the 6MWT against VO_{2peak} is evaluated in several studies, but the results are found inconsistent. Some studies have reported the 6MWT to have moderate to strong correlations with VO_{2peak}. For example, in persons with chronic obstructive pulmonary disease, the correlation coefficient is 0.64.[88] In persons with end-stage lung disease or pulmonary hypertension, the coefficient is 0.73[87] and 0.70[89] respectively. And, in persons with chronic cardiac failure, this value is 0.88.[90] However, other studies failed to demonstrate strong concurrent validity of the test against VO_{2peak}. Weak correlation coefficients of 0.37 and 0.48 were reported for persons with intermittent claudication[83] and for persons with congestive heart failure[91], respectively.

The convergent validity of the 6MWT as a measure of functional walking capacity has been compared with other indicators of functional capacity such as the Shuttle Walk Test (r=0.68).[92] Lower limb strength and standing balance have moderate relationships with 6MW distance, with correlation coefficients of 0.62[93] and 0.52[82], respectively.

4.4 Vertical Jump Test

Power is defined as the maximum force produced during a single rapid contraction, and is evaluated with the vertical jump test, known also as Sargent's test.[94] Participants are instructed to jump three times as high as possible. The maximum height jumped out of three trials is plugged in an already developed equation to determine leg peak power in Watts.[94]

This test is a reliable measure of power with a reliability coefficients of 0.97[111] and 0.98[112]. Criterion validity of the vertical jump test has been assessed in comparison with the cycling force velocity test, which is known as a valid measure of lower extremity peak power. Correlation coefficients range between 0.57 and 0.87.[113]

4.5 Partial Curl-ups

The partial-curl-ups is a test of muscle endurance. They evaluate an individual's ability to perform repetitive muscle contractions over time. Subjects will be instructed to execute as many consecutive curl-ups as possible during the specified time. [94]

Moreland and colleagues found a moderate intra-class correlation coefficient of 0.59 for this test.[108] A low correlation coefficient of validity of 0.234 was found by Kjorstad and colleagues.[109] A slightly higher correlation coefficient of 0.38 was found by Knudson and Johnston.[110]

4.6 Push-ups

The push-up is a test of muscle endurance, that evaluates an individual's ability to perform repetitive contractions over time [94].

For women, the knees are used as anchor points. This form of push-up is called the bent-knee push-up. The inter-rater reliability of bent-knee push-ups for women is 0.997, and the test-retest reliability is 0.83.[106] For men, the toes are used as pivot points during the push-up. Inter-rater reliability of this form of the test is 0.95, and the test-retest reliability is 0.91-0.93.[107]

In women, the validity of the bent-knee push-up against the bench press is 0.67.[106] For men, the validity of the push-up is 0.87.[107]

4.7 Grip Strength

Grip strength is defined as the force produced during a single maximum contraction against a resistance.[94] Standardized instructions and positioning are used during testing, since readings can vary depending on elbow position[100] as well as with verbal encouragement[101]. Norm-referenced age and gender-specific averages are available for maximum grip strength.[102, 103]

Mathiowetz et al. found the Pearson product-moment correlation coefficient for inter-rater reliability to be 0.996 for the right hand and 0.999 for the left.[104] The test-retest reliability for the right hand is 0.822 and for the left it is 0.915.[104] Bohannon and Schaubert calculated an intra-class correlation coefficient (for test-retest reliability) of 0.912 for the left hand and 0.954 for the right.[105] Similar results were found by Peolsson and colleagues, where intra-tester reliability ranged from 0.87 to 0.98, and inter-tester reliability was equal to 0.98.[101] Excellent reliability of this test was demonstrated in persons with MS as well, where inter-rater and test-retest reliability were 0.98 and 0.99 respectively.[47]

CHAPTER 5

Rationale and Objectives for First Manuscript

MS is a chronic, demyelinating disease of the central nervous system (CNS).[7] It is associated with multiple impairments of muscle, sensation, coordination, balance, speech, swallowing, cognition, and emotion.[114] These impairments lead to gradual deterioration of functioning in daily life. Therefore, optimizing the level of activity and participation through exercise is an essential part of management for persons with MS.[114]

Prior to 1995, intervention was mainly based on symptomatic treatment, such as steroids for relapses and baclofen for spasticity. However, in the past decade new disease modifying drugs such as interferon Beta and glatiramer acetate have been developed.[20] These are shown to be effective in modifying the course of MS. Clinical trials demonstrate that these therapeutic agents decrease the frequency of relapses and slow functional decline.[20-22] Furthermore, during the last 10 years, magnetic resonance imaging (MRI) has played a pivotal role in early diagnosis of the disease.[30] Prior to this, detection was simply based on the natural history of disability signs and symptoms. Therefore, due to these advances in neuroimaging and therapeutic treatments, in her article "*Setting the agenda for multiple sclerosis rehabilitation research"*, Mayo has proposed a new title: The New MS.[29] People are now diagnosed earlier, with milder forms of the disease that do not follow the same course as the old MS. Despite these advances in the diagnosis, treatment and slowing of progression of the disease, people still carry with them the image of the old MS.

It is important to map the course of the *New MS*. In order to better understand its impact on physical performance, more demanding tests of functional capacity are needed. An example of such a test is the maximal exercise test, which is the gold standard measure of exercise capacity. It is usually performed by using a treadmill or bicycle ergometer and is accepted as the best measure of cardio-respiratory capacity or fitness.[13]

Although this test is the most accurate measure of exercise capacity, it is not clinically useful because it requires access to equipment and a trained assessor who implements a standard testing protocol. It places significant physiological stress on the body and is resource intensive. Furthermore, in persons with neuromuscular symptoms such as fatigue, pain, and weakness during activities of daily living, maximal testing is usually discouraged.[75] This type of test may not be appropriate for people with MS, as motor impairments may prevent them from safely and successfully completing the test. Besides, recuperative capacity following exercise is often restricted for people with MS, who are counselled against strenuous exercise or overload,[115] as they may not recuperate for days or weeks. Apart from being very demanding and requiring specialized equipment and personnel, it may be a deterrent to retention of study subjects over time. Also, this test has no application for self-management as people with MS who are attempting to be more actively engaged in taking charge of their fitness level and to improve their exercise capacity cannot self-monitor with this test.

There are several clinically applicable tests that assess sub-maximal exercise capacity. These tests have been shown to predict maximum exercise capacity in different populations including those with health conditions. These tests can also be used to monitor progression in response to an exercise intervention. They are functional, easy to administer, inexpensive, and do not require subjects to exercise to exhaustion.

A well-established measure of sub-maximal exercise capacity is the six-minute walk test (6 MWT), which is often used as an alternative to maximal exercise testing in clinical settings. Experiments have demonstrated this tool to be a valid predictor of exercise capacity in persons with respiratory and cardiac diseases.[87-90]

The Canadian Physical Activity Fitness and Lifestyle Appraisal (CPAFLA) was created to evaluate fitness level of individuals from 15 to 69 years of age. It is compiled of multiple easy-to-administer tests of which norms have been developed.[18] These tests are: the modified Canadian aerobic fitness test (mCAFT), grip strength, push-ups, partial curl-ups, and vertical jump test. The mCAFT is a step test that measures aerobic capacity. Grip strength measures upper limb strength, whereas the vertical jump measures lower limb strength. Upper limb and abdominal muscle endurance are evaluated by performing push-ups and partial curl-ups.

By using the data from several of these functional sub-maximal tests (6MWT, grip strength, push-ups, partial curl-ups, vertical jump test, and mCAFT), a regression equation can be formulated to estimate the exercise capacity of patients with MS. This equation may be used in clinical settings to help assess and monitor maximum oxygen consumption and in research to evaluate the effect of exercise related interventions. Furthermore, it will allow people with MS to self monitor their exercise capacity and be more actively engaged in taking charge of their fitness level.

Therefore, the purpose of this study is to estimate, for persons with MS, the extent to which maximal exercise capacity can be predicted by the results on sub-maximal tests.

CHAPTER 6

Predicting Exercise Capacity Through Sub-Maximal Fitness Tests in Persons with Multiple Sclerosis

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INTRODUCTION

Multiple sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system (CNS).[1] It is the leading cause of neurological disability in young adults, [2] affecting two to four times as many women as men.[3] There are approximately 2.5 million people affected by MS worldwide.[4, 5] Although its exact aetiology remains unknown, evidence indicates that both genetic and environmental factors are involved with the disease onset.[6]

Over the last decade, significant advances in the diagnosis and management of MS have been accomplished. Prior to 1995, diagnosis was mainly based on abnormal neurological signs and symptoms, and management was aimed at reducing severity of acute relapses through the use of steroids. However, in the past 15 years magnetic resonance imaging (MRI) has played a pivotal role in the early diagnosis of the disease. [7] Besides, the introduction of disease modifying therapies (DMT) has allowed for better management of the progression of MS. [8-10] In her recent article "*Setting the agenda for multiple sclerosis rehabilitation research,*" [11] Mayo[11] has given a new name to people diagnosed after 1995, *The New MS*. Since the portrait of MS is changing, it is essential as she emphasizes, to better understand the impact of *The New MS* on people diagnosed with the disease.

Typically, MS is associated with multiple impairments of muscle, sensation, coordination and balance.[6] These and the stress of a serious diagnosis can lead to a decrease in physical activity which will have a concomitant effect on exercise capacity leading to a vicious cycle of inactivity, deconditioning and further disability. With the New MS, the course of this deterioration is not fully known and, as diagnosis is made earlier and pharmacological intervention reduces frequency of exacerbations, exercise capacity may by an early indication of impending disability. For people with the New MS, diminished exercise capacity could be a target for interventions targeting physical activity. In fact, promoting physical activity and healthy living is an essential part of chronic disease management.[12]

The current gold standard for testing of exercise capacity is a maximal exercise test which determines peak oxygen consumption (VO_{2peak}). Although it is the most accurate measure of physical fitness, it is used only in specialized laboratory settings due to its cost, equipment, and need of a trained assessor.[14] Furthermore, in persons with MS, neuromuscular symptoms such as fatigue, pain, and weakness may hinder them from safely and successfully completing the test.[14]

As maximal exercise testing is impractical and unfeasible in clinical settings, several sub-maximal tests have been developed as alternate means of measuring fitness. In comparison to maximal tests, sub-maximal exercise tests are clinically useful, as they are functional, easy to administer, inexpensive, and besides, do not require subjects to exercise to exhaustion.

In 1981 the most comprehensive study of fitness ever undertaken in Canada was a nationwide survey of more than 15,000 people. The data obtained from this study was compiled to produce the Canadian Physical Activity Fitness and Lifestyle Appraisal (CPAFLA). The CPAFLA evaluates the five components of fitness: aerobic fitness, body composition, flexibility, strength, and endurance. It is a standardized battery of sub-maximal tests with established norms to help interpret and evaluate fitness levels of individuals. [15]

Functional walk tests are also sub-maximal tests, which are simple and easy to administer. McGavin and colleagues introduced the 12-minute walk test (12MWT) to assess functional walking capacity in persons with chronic bronchitis.[14, 16] The distance ambulated in 12 minutes was recorded. However, after Butland et al demonstrated that similar results could be obtained in less time, the duration of the test was reduced to 6 minutes.[17] While several other measures of walking capacity are available, the 6MWT is recognized as one of the most accepted and well established tests used in clinical settings and in research. Experiments have demonstrated that the 6MWT correlates with VO_{2peak} in persons with respiratory[18] and cardiac diseases[19]; however, this association has not been assessed in persons with MS.

We hypothesized that by combining statistical data from the series of sub-maximal tests, we can formulate an equation that will estimate the fitness level of patients with MS. This equation may be used in clinical settings to help assess and monitor exercise capacity, as well as in research to evaluate the effect of exercise related interventions. Furthermore, it will allow people with MS to self monitor their exercise capacity and be more actively engaged in taking charge of their fitness level.

As such, the purpose of this study is to estimate, for persons with MS, the extent to which maximal exercise capacity can be predicted by the results on sub-maximal tests.

METHODS

Participants

This cross-sectional study was incorporated in a pilot study of the life-impact of the New MS. The available study population consisted of both men and women who had been registered after 1994 at the MS clinics of the Montreal Neurological Hospital, Centre Hospitalier de l'Université de Montréal (CHUM), and Clinique Neuro Rive-Sud. A centre-stratified random sample was drawn, and the sample comprised of 135 women and 48 men (53% of those contacted). A sub-sample of 21 men and 39 women who were able to perform the step test and who did not have a history of cardiac, pulmonary, orthopedic, or other impairments that would prevent participation in exercise testing, were selected from the pilot study sample. Subjects who had severe cognitive impairments or a relapse in the preceding month were excluded from participating in this cross-sectional study.

Procedure

The ethics committees of each participating hospital approved the study. Potential subjects were informed of the study by letter from the physician in charge of the MS clinic. A research coordinator subsequently contacted the subject to ascertain their interest in participating. For those agreeing, a questionnaire package with the consent form was mailed and an appointment for the evaluation was arranged.

All subjects attended two successive evaluation sessions. At the first, the sub-maximal fitness tests were carried out, and at the second one, the maximal exercise test was done with repeat testing of the push-ups, partial curl-ups, grip test, and jump test, in order to ensure that there were no important changes in patients' physical status. Subjects also rated their perceived health at both evaluations using the "feeling thermometer" of the EuroQol-5D (EQ-5D) to confirm that patients' health status did not change. Subjects were instructed to indicate their health condition on a scale from 0 to 100, the former showing the worst imaginable health state, the latter marking the best imaginable health state.

Measurement

Subject characteristics: Personal factors such as age, sex, height, weight and smoking status were recorded on the day of testing. Duration of the disease, type of MS, and patients score on Expanded Disability Status Scores (EDSS) were determined from medical charts. Balance was assessed using a MS specific balance scale called Equi-Scale, created using Rasch modeling from the Tinetti Performance Oriented Balance Scale and the Berg Balance Scale. Spasticity of the lower and upper limbs was assessed using the Modified Ashworth Scale (MAS). Fatigue and muscle pain were measured with a 10 cm visual analogue scale (VAS) with anchors of no fatigue to severe fatigue and no pain to worst pain imaginable.

Exercise capacity: Peak oxygen consumption (VO_{2peak}) was determined using an incremental graded cycle ergometer test. The person was properly seated on the bicycle with an upright posture, hands positioned on the handlebars, and seat adjusted for adequate knee extension. Heart rate was recorded each minute. Respiratory exchange ratio (RER), which is the ratio of carbon dioxide output to oxygen uptake, was continuously measured and analyzed by placing a mask over the individual's face that was connected to a metabolic cart. Perceived exertion was evaluated using the Borg Rating of Perceived Exertion (RPE) 6-20 scale. All persons started the test at a minimal workload of 10W with a gradual increase of 10W per minute. They were instructed to pedal at a constant frequency of 60rpm throughout the test. The test was terminated when the subject was not capable of maintaining a pedaling frequency of at least 45rpm. Maximum oxygen uptake was expressed as absolute (L/min) or relative to body weight (ml/kg/min).

The Modified Canadian Aerobic Fitness Test (mCAFT): This is a multi-stage step test that assesses sub-maximal exercise capacity. Standardized instructions and procedures as outlined in the CPAFLA manual were used. Subjects were asked to perform a series of stepping sequences on a double 20.3-cm step in time with a musical cadence. [20-22] Starting stage or stepping sequence was determined according to the patient's age. Each stage lasted 3-minutes and became progressively more challenging. Subjects completed all the stages necessary to achieve 85% of their age predicted maximum heart rate.[23] An oxygen uptake value for the final stepping stage was taken from the Canadian Standardized Test of Fitness Operations Manual. The mCAFT has been shown to have a high degree of reliability[24] and validity[20].

The Six-Minute Walk Test (6MWT): The 6MWT was performed in an enclosed 10 to 15m corridor. Individuals were instructed to walk as far as possible in six minutes at their own pace. They could rest at any time during the test but were encouraged to resume walking as soon as they were ready to do so. The number and duration of rests, as well as the total distance ambulated was recorded.

Standardized instructions and encouragements were used.[25] The 6MWT has high reliability[26-36] and moderate validity[37].

Vertical Jump Test: The vertical jump test, also taken from the CPAFLA, was administered to evaluate lower extremity power. In order to measure initial reach height, while the feet are flat on the floor, subjects reached as high as possible with the fingers and elbow of the dominant hand fully extended. The participants then jumped as high as possible, touching the wall at the peak height of their jump. The vertical jump height was determined by subtracting the initial reach height from the jump height. The maximum height jumped out of three trials was recorded in centimetres. Peak leg power can be estimated from height jumped through the equation reported by Sayers. [23, 38, 39]

Partial Curl-ups: The partial curl-ups are also a test of muscle endurance. During this test, subjects were instructed to execute as many consecutive curl-ups as possible at a rate of 25/min for a maximum of 1 minute, following the cadence provided on a metronome. From a supine position with knees bent at 90^{o}, subjects were asked to slowly curl-up the upper spine until the middle finger tips of both hands have reached the 10cm mark on the mat, and then to slowly return to the mat. [23, 39] The guidelines set out by the CPAFLA were used.

Push-ups: The push-ups are a test of muscle endurance that evaluates an individual's ability to perform repetitive contractions over time.[23] Subjects were instructed to perform as many consecutive push-ups to fatigue without any time limit. For anchor points males used their toes, females their knees. The test was terminated when subjects were seen to strain forcibly or were using compensatory techniques.[39] Guidelines were implemented according to the CPAFLA manual. Norm-referenced age and gender-specific averages are available for this test.

Grip Strength: Grip strength was measured using the Jamar™ dynamometer. Standardized instructions and positioning were used and three consecutive trials for each hand were recorded.[40, 41] Grip strength has excellent reliability.[26, 40, 42, 43]

Data Analysis

The primary outcome measure was peak oxygen consumption (VO_{2peak}), assessed using a graded cycle ergometer test. The predictor variables were the mCAFT, the 6MWT, grip strength, push-ups, partial curl-ups, vertical jump height, age, height, and weight. The classification and measurement of these variables are presented in Table 6.1.

Descriptive statistics were used to characterize the participants and verify the distribution of variables. Patients' characteristics and maximal and sub-maximal test scores were summarized using the mean values and standard deviations (SD).

Spearman and Pearson correlation coefficients were used for categorical and continuous variables, respectively. Unlike the Pearson's correlation, Spearman's correlation is rank-ordered and distribution free. Therefore, we thought that it would be more appropriate if we would use Spearman's correlation rather than Pearson's, for the push-ups and the curl-ups, as they were not normally distributed.

The Student's t-test was used to compare results between the first and second evaluation on the push-ups, curl-ups, grip strength, and jump test. Muscle pain, fatigue, and perceived health status were also reassessed during the second session to ensure that patients' physical status did not change since the initial visit.

The potential for confounding from sex, muscle pain, fatigue, balance, disease severity and spasticity were tested using simple linear regression. Each potential confounding variable was assessed for its relationship with the outcome (VO_{2peak}) and with each of the predictor variables (age, height, weight, 6MWT, mCAFT, grip strength, push-ups, curl-ups, and jump height). Those variables found to have a significant effect on both the outcome and one of the explanatory variables was added to the final predictive model.

Forward stepwise multiple linear regression was performed to identify the best predictive model of exercise capacity. Knowing that the mCAFT is a predictor of VO_{2peak} [20-22, 44] we first performed simple linear regression of the outcome with the mCAFT. Right after this, we selected the predictor variable that increased the R-square most. We have repeated this procedure until we have failed to explain any additional variability in the outcome.

Regression diagnostics, including the Shapiro-Wilk statistics and residual-by-predicted plots were generated to verify the assumptions of normality, homoscedasticity and linearity. Regression diagnostics were also used to check for collinearity and outliers.

All statistical analysis was carried out using the Statistical Analysis Systems (SAS) Version 9.1.

RESULTS

Patients

Initially, a total of 60 subjects with MS were evaluated. However, due to technical problems with calibration of the cycle ergometer, the result of one subject was distorted, which left us with 59 subjects to be analysed. The average age was 39 years, and the average EDSS score was 1.4. Patient characteristics are presented in Table 6.2. The median number of partial curl-ups performed was 23 and median number of push-ups was 3. The mean jump height for the sample was 26 cm, and the mean grip strength of the right and left hands combined was 75 kg. Distance walked during the 6MWT was 572 meters, and the average oxygen uptake for the mCAFT was 1.64 L/min. The mean VO_{2peak} was 27.6 ml/kg/min or 1.9 L/min. The average percentile ranking of the participants in comparison to norms is presented in Table 6.3. For the 6MWT, since there are no norms, percent walked of age-predicted distance using an already developed multiple linear regression equation was calculated.[52]

Comparison of health status and physical performance across time

Subjects, prior to their graded bicycle test, performed the push-ups, curl-ups, grip strength, and jump test a second time. The average number of days between the two evaluation sessions was 16 with a standard deviation of 7 days. There was no difference in the number of curl-ups carried out between the first and second evaluations. However, during the second evaluation, subjects performed worse on the jump test, and better on the push-ups and grip test. No difference was noted in level of muscle pain, fatigue and perceived health status between the two days. Results are presented in Table 6.4.

Spearman's and Pearson's correlation coefficients

Table 6.5 displays the correlation coefficients between the potential predictor variables and the outcome. VO_{2peak} measurements were recorded as absolute (L/min) and relative to body weight (ml/kg/min). All sub-maximal tests were found to be significantly correlated with VO_{2peak} ($p<0.05$).

Age and 6MWD were weakly correlated with absolute VO_{2peak} (L/min) ($r = -0.29$ and $r = 0.28$ respectively). The push-ups, partial curl-ups and the jump test were found to have moderate correlations with VO_{2peak} ($r = 0.49$, 0.43 and 0.55, respectively). The mCAFT and grip strength had the highest correlation coefficients of 0.73 and 0.76 with VO_{2peak}.

On the other hand, when VO_{2peak} was reported relative to body weight (ml/kg/min), the mCAFT was the only exposure variable with a correlation coefficient above 0.7. All other sub-maximal tests were moderately correlated with the outcome.

Confounding variables

The possible confounding variables were sex, pain, fatigue, present smoking status, disease severity, and spasticity. Simple linear regression of each one against the outcome and exposure variables was performed. Current smoking status, treated as a binary variable (currently smoking or not), was found to be statistically significant with the jump test ($p = 0.04$) but not with $VO_{2peak,}$ explaining approximately 7% of the variance in jump height.

Spasticity, measured by the MAS, was treated as a binary variable (presence or absence of spasticity). It explained 13% of the variability in the 6MWT ($p = 0.006$). Sex was significantly associated with most of the predictor variables and the outcome. A confounding variable must be associated with *both* the exposure variable(s) and the outcome, but not be in the causal pathway. Therefore, sex was only included in the multiple linear regression model as a confounding variable.

Multiple linear regression analyses

Table 6.6*a* and 6.6*b* display the results of the multiple linear regressions of the exposure variables on absolute and relative VO_{2peak}. Along with the sub-maximal tests, age, height, weight and sex were also included in the model. When all of these variables were modeled together, the mCAFT, grip strength, and body weight emerged as significant predictors. While controlling for sex, these three variables explained 74% ($p<0.001$) of the variability in absolute VO_{2peak} (L/min).

The same group of variables, excluding body weight, were modeled together with relative VO_{2peak} (ml/kg/min) as the outcome. This time, while controlling for sex, the mCAFT and the 6MWT surfaced as significant predictors, explaining 55% ($p<0.0001$) of the variability. The standardized parameter estimates, un-standardized parameter estimates, and their p-values are presented in the tables.

DISCUSSION

The average VO_{2peak} of this sample was 27.6 with a standard deviation of 7.25 ml/kg/min. This value is considerably low if compared to normal healthy individuals, ranking below the 25th percentile for both men and women.[15] Interestingly, despite having mild levels of disability, (mean EDSS score 1.4), this sample demonstrated marked reductions in exercise capacity. Bjarnadottir et al found similar results in their study on the effects of moderate exercise in mild MS patients with an average EDSS of 2.0. They conducted a randomized controlled trial with a control group of 10 MS subjects and an intervention group of 6 MS subjects. Their recordings at baseline were, 27.3 ml/kg/min for the control group and 23.4 ml/kg/min for the intervention group. Although they studied a small sample of patients, their findings are very similar to those of ours. Bjarnadottir also evaluated exercise capacity for men and women separately. For their male participants, the average VO_{2peak} was 33 ml/kg/min, and for their female participants it was 21 ml/kg/min. Likewise, in our study the mean VO_{2peak} for the male participants, was 32±6.4, and for the female participants it was 25.7±6.6 ml/kg/min.

Romberg et al. studied a larger group of patients in a cross-sectional study on the extent to which exercise capacity can be predicted by disability and physical activity. Their sample consisted of 34 male patients and 61 female patients with average EDSS scores of 3 and 2.2, respectively. The average VO_{2peak} value for males was 27±5.2 standard deviations, and for females it was 21.7±5.5. It is not surprising that their findings were lower than ours, since their sample consisted of patients with slightly greater levels of disability.

One of the selection criteria for this study was to include only subjects diagnosed after 1995. This was the year that disease modifying therapies and magnetic resonance imaging (MRI) played crucial roles in the diagnosis and management of the disease. We evaluated the impact of the disease in this group of patients who had been diagnosed during the past decade. One would probably assume that with these new advancements, the impact of the disease on exercise capacity would be of a lesser extent; but, interestingly our findings were not able to support this. Although these patients had mild disability levels, they still demonstrated significantly reduced exercise capacity. Furthermore, they also demonstrated a considerable decrease in muscle strength and endurance. As far as the push-ups and the jump test were concerned, they ranked, when compared to norms, below the 30th percentile. They had slightly better results for grip strength and the curl-ups, ranking at the 50th and the 60th percentiles, respectively. According to the EDSS classification system, our sample would be categorized as being fully ambulatory with minimal neurological signs. This raises an issue with the EDSS as a comprehensive indicator of MS severity because the participants, even with minimal disability, had very poor exercise capacity. The EDSS places strong emphasis on ambulation, especially at the middle range of the scale (EDSS 4.5 to 6.5). As mentioned in the review by Dalgas and colleagues, these reductions in physical capacity may be due to the disease process per se (changes in the CNS) or due to the increased physical inactivity levels found in these patients.[45]

Functional walking capacity, measured by the 6MWT, correlated weakly with VO_{2peak} ($0.23 \leq r \geq 0.48$). The correlation of this sub-maximal test against VO_{2peak} has been evaluated for different diseases such as cardiac and pulmonary conditions. In persons with end-stage lung disease or pulmonary hypertension, the coefficient is 0.73[36] and 0.70[46]. Also, in persons with chronic cardiac failure, this value is 0.88.[19] However, other studies, like ours, failed to demonstrate strong concurrent validity of the test against VO_{2peak}. Weak correlation coefficients of 0.37 and 0.48 were reported for persons with intermittent claudication[32] and for persons with congestive heart failure[47], respectively. Our findings would suggest that the 6MWT is a measure of functional walking capacity as indicated by Eng for stroke rather than being a measure of exercise capacity.[48]

As we were concerned that the sub-maximal and maximal exercise tests could lead to excessive fatigue and an exacerbation of symptoms, the assessments were conducted on different days. However, there were few important differences on the fitness test scores between the two evaluations. For example, subjects performed, on average, one more push-up on the second day and some of this difference may be explained by measurement error because the assessor administering the test at the first evaluation did not always administer the test at the second evaluation. A better measure to confirm that participants did not have a relapse, was the EQ-5D VAS of perceived health status. Subjects were asked to provide a global rating of their current health status from 0 to 100, where 0 was marked by the worst imaginable health state, and 100 as the best imaginable health state. As we found no significant differences in patients rating of their health status between the two sessions, we feel the data from the two different testing days can be combined.

For the step test, there were seven participants who were not able to complete all of the stages that were necessary to attain 85% of their age-predicted maximum heart rate. Although they all performed at least one stage of the test, due to problems with coordination and motor fatigue of the lower extremities, they could not continue further. The multiple linear regression analysis was carried out first with these patients included in the model, and then excluded from the model. Interestingly, we were able to explain the same amount of variance with them excluded from the model, inidicating that the step test was still a good predictor of VO_{2peak}, even when patients were not able to reach 85% of the maximum capacity.

Two models of multiple linear regression were performed, one with relative VO_{2peak} and another with absolute VO_{2peak}. For VO_{2peak} relative to body weight, the mCAFT alone explained 48% of the variability in the outcome. The 6MWT surfaced as the only predictor variable, when combined with the mCAFT, that explained the most additonal variability in VO_{2peak}. Together these two variables described 55% of the variance in the outcome.

In the multiple linear regression analysis with absolute VO_{2peak}, the mCAFT, grip strength and body weight emerged as the only significant predictors in the model. Altogether, these three variables explained 74% of the variability in VO_{2peak} (L/min). Interestingly, among all the fitness tests that were performed in this study, in addition to the mCAFT, grip strength was the only submaximal test that was able to explain any further variability in VO_{2peak}. Therefore, grip strength is not only a convenient and simple measure of upper limb function, but also a good indicator of overall health. As has been shown, it can differentiate between high and low levels of health, and detect persons at risk for developing physical disability.[49, 50] Undoubetdly, the push ups, curl-ups and jump test were also regarded as important measures of fitness; but, when modeled together with grip strength and the mCAFT, they failed to explain any additional variability in VO_{2peak}.

Limitations

As this study was cross-sectional in design, subjects were assessed at one point in time and hence may not necessarily reflect all time points. Furthermore, as only patients with the New MS were included, this sample may not be generalized to all MS patients. In addition, our inference is to those people who can perform the fitness tests; the study of exercise capacity for the New MS population would probably be lower, as 25% of the entire sample of 185 participants could not do the mCAFT. Moreover, during the graded bicycle test, individuals might not have reached their true VO_{2peak} due to the presence of musculoskeletal impairments such as pain and fatigue. The subject's level of motivation could have also affected VO_{2peak} results, especially between men and women, as the men performed better than the women. But then again, gender differences in exercise capacity are inevitable, because men are reported to have 15 to 30% greater exercise capacity than women.[51]

Conclusion

The mCAFT, grip strength, and body weight are strong predictors of exercise capacity. These measures may be used, in clinical settings, to help assess and monitor exercise capacity, and in research, to evaluate the effects of exercise related interventions.

TABLE 6.1 Classification and Measurement of Independent Variables Entered into the Regression Model

Exposure Variable	Measurement Scale	Units/Scoring/Coding
Socio-demographic Variables		
Sex	Binary	0 = male 1 = female
Age	Continuous	Years
Height	Continuous	Centimetres
Weight	Continuous	Kilograms
Sub-maximal performance tests		
mCAFT (step test)	Continuous	Litres per minute (L/min)
Six-minute walk distance	Continuous	Meters
Vertical jump height	Continuous	Centimetres
Partial curl-ups	Binary	0 = 0 to 15 curl-ups 1 = 16 to 25 curl-ups
Push-ups	Binary	0 = unable to do a push-up 1 = able to do one or more push-ups
Grip strength	Continuous	Kilograms

TABLE 6.2 Demographic and clinical characteristics of study participants

Characteristic	Participants (n=59)
Age in years, mean (SD)	39 (8.8)
Sex, No. (%)	
Male	20 (34)
Female	39 (66)
Height in cm*, mean (SD)	169.4 (9.1)
Weight in kg*, mean (SD)	71.2 (15.5)
BMI in kg/m^2*, mean (SD)	24.8 (4.8)
Current smoking status*, No. (%)	
Yes	15 (25)
No	44 (75)
Type of MS†, No. (%)	
Definite MS	55 (93)
Clinically Isolated Syndrome	4 (7)
EDSS score†, median (IQR)	1.5 (0 to 2)

SD, standard deviation; No., number; BMI, Body Mass Index;
EDSS, Expanded Disability Status Scale; IQR, Inter-quartile range
*Self-reported by participant
†Obtained from medical charts

TABLE 6.3 Participants percentile ranking on the fitness tests compared to norms

Measure	Mean Percentile ranking (SD)
Six-Minute Walk Test	81 (12)
Curl-ups	61 (38)
Grip strength	49 (32)
mCAFT	45 (24)
Jump test	29 (21)
VO_{2peak}	23 (24)
Push-ups	16 (19)

SD, Standard Deviation

TABLE 6.4 Fitness test scores, fatigue, muscle pain and perceived health status at first and second evaluation

Variable	Mean (SD) Time 1	Mean (SD) Time 2	P-value
Jump height (cm)	26.1 (10.2)	25.0 (10.3)	0.021*
Curl-ups (#)	15.9 (10.7)	15.6 (10.7)	0.36
Push-ups (#)	5.7 (6.6)	6.5 (6.9)	0.026*
Grip strength (kg)	75.7 (24.3)	78.5 (24.5)	0.003*
Fatigue (0 to 100)	2.5 (2.3)	1.9 (2.1)	0.053
Muscle Pain (0 to 100)	0.6 (1.4)	0.8 (1.5)	0.48
Health today (0 to 100)	80.3 (12.6)	82.0 (15.1)	0.35

*p<0.05

TABLE 6.5 Correlation matrix of all variables in model with relative VO_{2peak} (ml/kg/min) and absolute VO_{2peak} (L/min) as the outcome (n=59)

Variable	Age	Height	Weight	mCAFT	6MWT	Jump Height	Curl-ups	Push-ups	Grip strength
Height	-0.18								
Weight	0.16	0.44‡							
mCAFT	-0.36†	0.59¶	0.23						
6MWT	-0.40†	0.21*	-0.24	0.34†					
Jump	-0.38†	0.50¶	0.12	0.64¶	0.42‡				
Curl-ups	-0.28*	0.23	0.09	0.50¶	0.42‡	0.48¶			
Push-ups	-0.33*	0.30*	0.07	0.63¶	0.33†	0.63¶	0.48¶		
Grip	-0.16	0.68¶	0.57¶	0.61¶	0.19*	0.61¶	0.48¶	0.46‡	
VO_{2peak} (L/min)	-0.28*	0.68¶	0.52¶	0.76¶	0.25*	0.52¶	0.43‡	0.49¶	0.76¶
VO_{2peak} (ml/kg/min)	-0.45‡	0.46¶	-0.11	0.70¶	0.48¶	0.51¶	0.51¶	0.57¶	0.45‡

*$p<0.05$ †$p<0.01$ ‡$p<0.001$ ¶$p<0.0001$, Spearman correlation used for the push-ups, Pearson correlation used for all others

TABLE 6.6a Multiple linear regression model for absolute VO_{2peak} (L/min)

	Unstandardized coefficients Beta	Standard Error	Standardized coefficients	P value
Step test (L/min)	1.091	0.180	0.31	<0.0001
Grip strength (kg)	0.009	0.003	0.22	0.004
Body weight (kg)	0.009	0.004	0.14	0.02
Sex	0.067	0.180		0.71

Outcome variable: VO_{2peak} in L/min. Total $R^2 = 0.74$, $p<0.0001$
Intercept is -1.176, standard error 0.589, p=0.05
Standardized coefficient = Beta x 1 Standard Deviation

TABLE 6.6b Multiple linear regression model for relative VO_{2peak} (ml/kg/min)

	Unstandardized coefficients Beta	Standard Error	Standardized coefficients	P value
Step test (L/min)	16.3	3.24	4.89	<0.0001
6MWT(m)	0.02	0.0076	1.84	0.0079
Sex	1.78	1.95		0.3665

Outcome variable: VO_{2peak} in ml/kg/min. Total $R^2 = 0.55$, $p<0.0001$
Intercept is -11.83, standard error 6.41, p=0.734
Standardized coefficient = Beta x 1 Standard Deviation

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CHAPTER 7
Integration of Manuscript 1 and 2

7.1 Research objectives of manuscript 1 and 2

Manuscript 1:

It aims to estimate the extent to which sub-maximal tests predict exercise capacity in persons with MS.

Manuscript 2:

It aims to estimate the extent to which physical capacity predicts perceived health status in persons with MS.

7.2 Integration of manuscript 1 and 2

MS is a chronic disease with an unpredictable course that impacts significantly on physical performance. Exercise or fitness has become an essential part of management and health promotion for persons with MS. Rehabilitation is aimed at both reducing impairments such as weakness, as well as increasing activity and participation.

Health-related quality of life (HRQL) is greatly reduced in MS, as it impacts health perception and capacity to perform daily activities. Therefore, improving HRQL has become an important goal of all health care interventions. It is essential to evaluate and understand patients' own perceptions of the impact of symptoms on their overall health status and their well-being. Therefore, since the first manuscript has assessed the impact of the disease on exercise capacity through objective measures, the second manuscript will observe its impact from the patients' perspective. Assessing the patients' perspective can provide additional information and insight into the understanding of disease activity and severity.

CHAPTER 8

8.1 A literature review of perceived health status and health-related quality of life

Health related quality of life (HRQL), in effect, reveals the patients' perspective on health and well-being. HRQL is defined as "*the value assigned to duration of life as defined by the impairments, functional status, perceptions, and opportunities influenced by the disease, injury, treatment, and policy*"[116]. Areas such as economics, family life, and employment, which are outside the purview of the health care system, are not included in HRQL.[117]

Improving HRQL has become an important objective of all health care interventions involving patients with chronic diseases such as MS. The management of these diseases are rehabilitative or preventative in nature, rather than curative. Thus, research focuses on evaluating domains such as life-style and productivity, constructs that are best obtained from patients directly.[118] The importance of assessing disease activity and impact from the patient's perspective has been recognized and implemented in clinical practice and research. Clinicians assess a condition from the perspective of the impact on body functions, but patients focus on the changes that they face in their everyday lives. [119] Most performance-based measures, such as muscle strength and spasticity, do not offer any explanation of MS on daily functioning. Therefore, patient-reported outcomes (PROs), defined as "*patient's report of a health condition and its treatment,*" are important in understanding patient's perspectives on the impact of the disease on function and well-being.[119]

Conceptual frameworks have been developed to explain HRQL and its components. There are two commonly used models or frameworks: are the International Classification of Functioning Disability and Health (ICF) and the Wilson-Cleary Model (WCM).

In 2001, the World Health Organization (WHO) approved the ICF as an addition to the International Classification of Diseases (ICD-10), the international standard diagnostic classification for health management purposes and clinical use.[120] While the ICD-10 has diagnosis and physiological medical status of persons at its core, the ICF has functioning at its centre. The ICF is a biopsychosocial model that consists of two components; each part is further classified into sub-sections (Figure 8.1). The first component is *Functioning and Disability*, which includes: *body function, body structure,* and *activity and participation.* The second component is *Contextual Factors*, which includes *environmental factors* and *personal factors.* These factors are bi-directionally associated with each other and define health status of individuals.[121] This classification has been translated into multiple languages and acknowledged by health experts around the globe.

The Wilson-Cleary Model (WCM) is another commonly applied conceptual framework of HRQL (Figure 8.2). It explains the relationship between clinical and physiological variables with HRQL. It proposes that physiological factors, symptom status, functional status, general health perception and overall QOL are associated with each other, and that they are all dimensions of HRQL. For the second part of this thesis, by using the WCM as a conceptual framework, we will be evaluating the relationship between functional status and general health perception in patients with MS.[122, 123]

The WCM is a medical model that provides a framework of the relationship between diagnosis and therapy. The ICF, on the other hand, is a biopsychosial model that focuses on functioning as a major component of health. The combination of these two models can also be used as a conceptual framework. As demonstrated in Figure 8.3, there is considerable overlap or similarities between the two models. Body functions and structure in the ICF, correspond with biological and physiological variables and symptom status in the WCM. Activity and participation of the ICF is equivalent to functional status of WCM. The WCM includes general health perception and overall QOL, and the ICF considers these variables to be independent from functioning and disability. The ICF model defines QOL as one's personal satisfaction with his or her functioning. By combining these two models, the effectiveness of interventions can be realized from both medical and rehabilitative standpoints.

MS patients have significantly lower levels of HRQL than the general population.[124] Generic and MS specific measures of health status have been developed and applied in clinical research to evaluate the impact of the disease on the individual. An example of a commonly used generic measure is the Medical Outcomes Study Short Form-36 Health Survey (SF-36). This measure of health status has been used in both healthy individuals and persons with chronic diseases. It consists of the following eight components: physical functioning, role-physical functioning, bodily pain, general health perceptions, vitality, social functioning, role-emotional functioning, and mental health. The EQ-5D is another well-established and widely used generic instrument of HRQL. It includes 5 domains; mobility, capacity for self-care, conduct of usual activities, pain/discomfort and anxiety/depression. The patient responds by selecting one of three different levels of problem severity (none, moderate and severe/extreme) for each of the five health domains. Following this, the patient then evaluates his or her general health state by using a visual analogue scale (VAS).

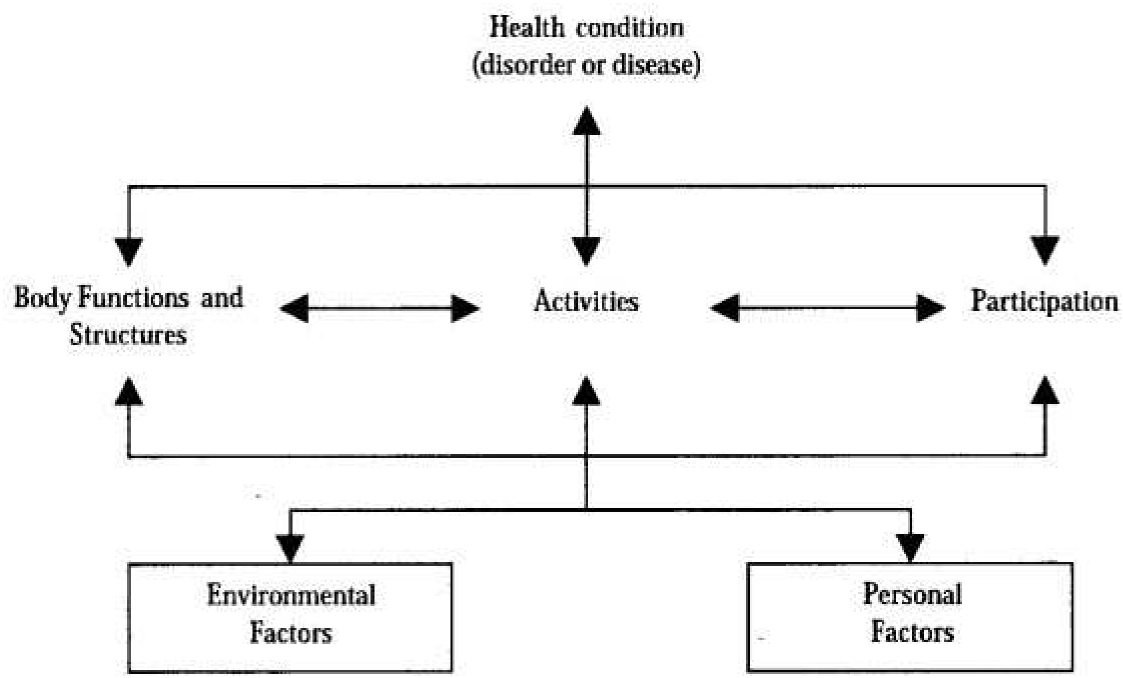
Perceived health status, also known as general health perception, is an important component of HRQL that is measured by both of the instruments described above. Both HRQL and perceived health status incorporate the concept of health, which is defined by the WHO as, "*a state of complete physical, mental, and social well-being, and not merely the absence of disease or infirmity*[125]." However, from the perspective of patients, these two concepts have different meanings. For patients, QOL or HRQL is mostly explained by psychological functioning, and perceived health by physical functioning.[125] The first question in the SF-36 measures perceived health status, and is formulated as, "In general, would you say your health is…,” with five nominal response options ranging from excellent to poor. The VAS of the EQ-5D is also a measure of general health perception ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).

Perceived health status is easy to measure and can also provide useful information concerning a person’s well-being and overall HRQL. Nortvedt et al investigated perceived health status as a predictive factor for the development of disease. The SF-36 was administered on 97 patients with MS, who were followed up for one year. The first question of the SF-36 was used to measure perceived health, and the Expanded Disability Status Scale (EDSS) to measure disability. Patients who evaluated their health as “poor” or “fair” had twice the chance of experiencing a worsening of EDSS score 1 year later, versus patients who evaluated their health as “good”, “very good”, or “excellent”. This study confirms that a patient-reported measure of perceived health is important in providing additional information on disease activity in patients with MS.[126] As mentioned earlier, general health perception can as well be measured using the VAS of the EQ-5D. In a study by Parkin and colleagues, the VAS of health status was found to be sensitive to the presence of symptoms (e.g. weakness, sensation, bladder, bowel, and fatigue), their severity and their type.[127]

Considering the wide range of symptoms and health-problems that accompany this disease, assessing patients’ perception of their health status has become an increasing area of interest in MS research. It is essential to evaluate patients’ own perceptions of the impact of symptoms on their overall health status and their well-being. The understanding of this matter will make significant contributions in designing treatment approaches in the rehabilitation of patients with MS.

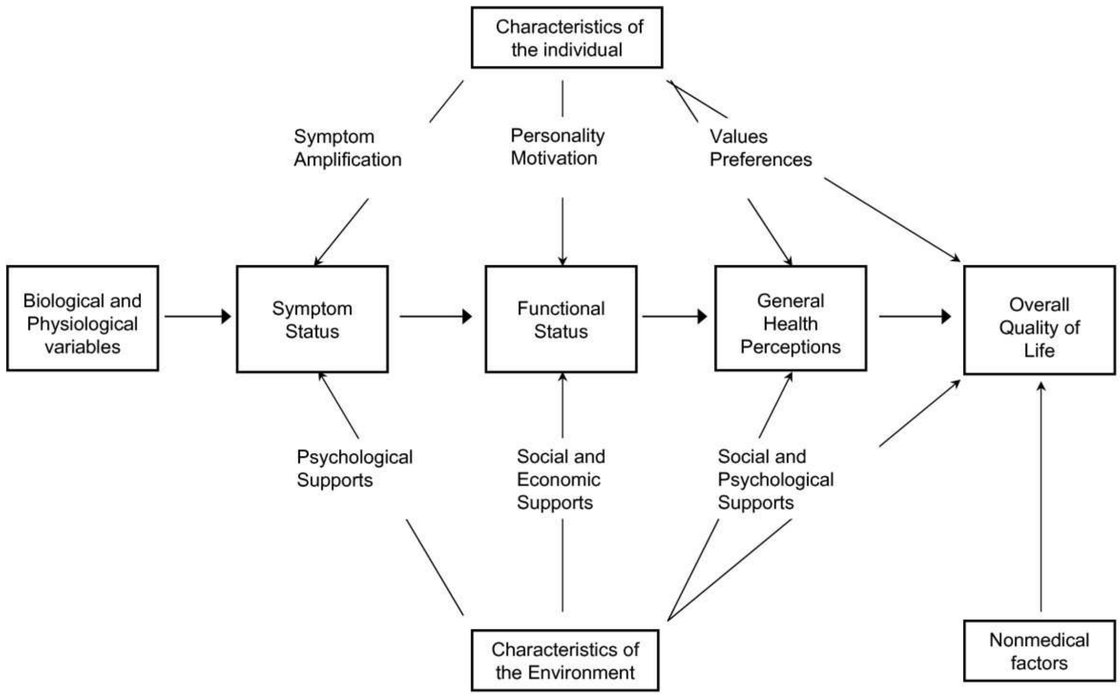
Figure 8.1

International Classification of Functioning, Disability and Health (ICF) model.



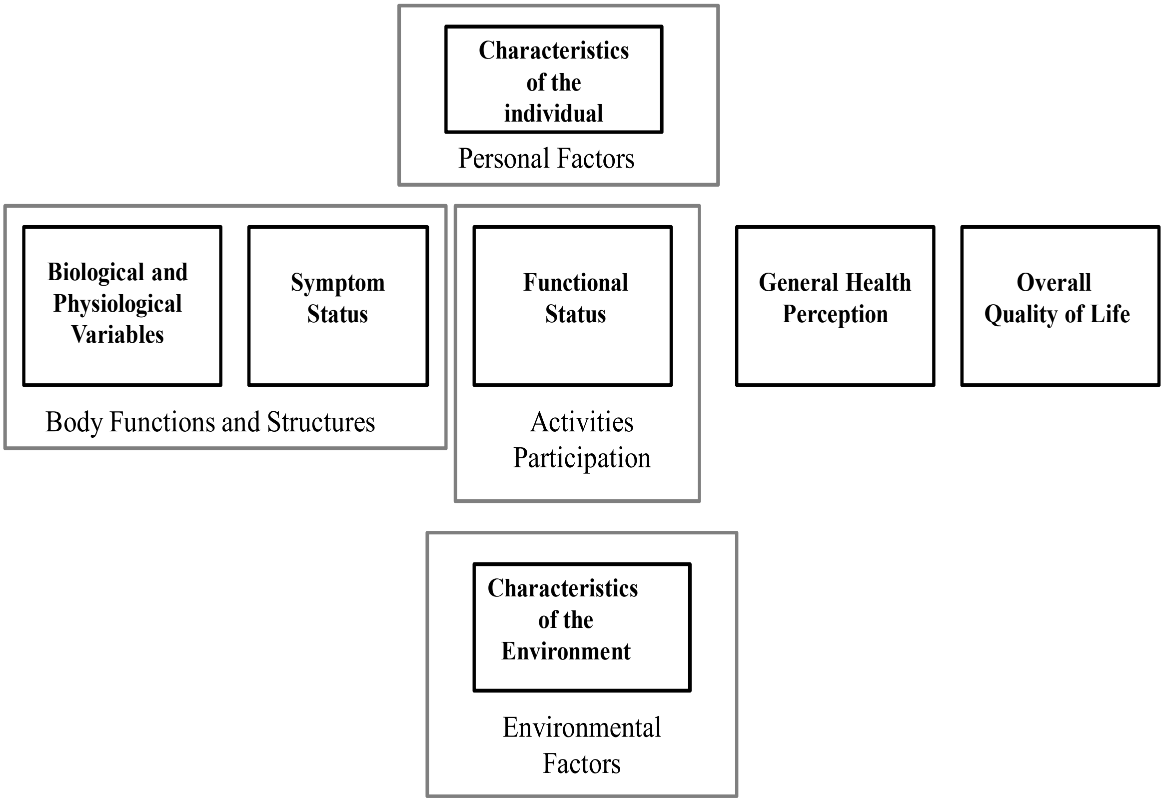
Taken from: World Health Organization (WHO) (2001). International Classification of Functioning, Disability and Health. Geneva, Switzerland: WHO.

Figure 8.2 The Wilson & Cleary Model



Taken from: Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA 1995; 273(1):59-65.

Figure 8.3


Characteristics of the individual
Personal Factors
Biological and Physiological Variables
Symptom Status
Body Functions and Structures
Functional Status
Activities Participation
General Health Perception
Overall Quality of Life
Characteristics of the Environment
Environmental Factors

8.2 Relationship between physical capacity and self-perceived health in persons with multiple sclerosis

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Introduction

Multiple sclerosis (MS) is a chronic disease causing demyelination in the central nervous system (CNS). [1] MS is the leading cause of neurological disability in young adults[2], affecting two to four times as many women as men[3]. The aetiology of this neurological disease is unknown, and its course is difficult to predict. It leads to a variety of symptoms, such as fatigue, weakness, altered sensation, and cognitive impairments.[4]

Perceived health status, also known as self-rated health, is an important marker of the multi-dimensional concept of health. The World Health Organization (WHO) defines health *"a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."* [5] Perceived health status is a global assessment of a person's general state of health.[6] It provides clinicians and researchers with insight into how individuals perceive their overall health status.

Perceived health status has been used for a variety of purposes, especially for well-being and health services utilization, and as such it is indeed an important predictor of mortality and morbidity.[7] In patients with MS, perceived health status has been shown to be a predictor of disease progression, and sensitive to the presence of a wide range of symptoms such as weakness, sensation, bladder, bowel, and fatigue.[8]

The Visual Analogue Scale (VAS) is a widely used tool for the measurement of health. It can be adapted to different situations or contexts, including general health perception. It is a straight line with short descriptors at each end that describe the variable being quantified. The theory underlying the VAS is that persons have basic value sets that are expressed as responses to the visual stimuli provided.[8] The VAS has several good qualities in terms of practicality, reliability and adaptability.[8]

Perceived health status or self-rated health may be influenced by several factors that occur as a result of the disease process. It is the individual's perception of the impact of the disease on his or her daily life. It is a simple means of obtaining information and providing insights into a patient's well-being and HRQL.

MS is a chronic debilitating disease that can have a severe impact on one's functional capacity, which in turn affects perceived health status and overall HRQL. In the general population, the association between physical capacity and perceived health status has been examined[6]. The evidence demonstrates that physical capacity predicts self-perceived health; however, this has not been addressed in persons with MS. The understanding of this matter will make important contributions in designing treatment approaches in the rehabilitation of MS.

Therefore, the purpose of this study is to estimate the extent to which physical capacity predicts perceived health status in persons with MS.

Methods

Subjects:

The data for this study comes from a pilot study of the life-impact of the New MS. The available study population consisted of both men and women who had been registered after 1994 at the three participating MS clinics in Greater Montreal, Quebec, Canada. From a pool of 5000 patients, a centre-stratified random sample of 550 patients was drawn, of which 394 were contacted. From those who were contacted, 185 persons responded. Respondents and non-respondents were compared, and no statistically significant differences were found between the two groups on socio-demographic characteristics. Two people who did not attend the evaluation session were excluded from the present study. The final sample comprised of 135 women and 48 men. Letters of study introduction were sent from the Director of the specific MS clinic to those selected, describing the project and inviting the person to participate. The letter indicated that a research assistant (not involved with patient care) would be contacting them to provide additional information and arrange for an appointment. Persons who did not want to take part in the project were instructed to leave a message by telephone or email informing that they should not be contacted. A questionnaire package with the consent form was mailed to the persons who had stated their willingness to participate. Later they were contacted by telephone to arrange an appointment for the evaluation. Inclusion criteria were diagnosis of MS or Clinically Isolated Syndrome (CIS) after 1994. Persons with history of heart disease, arthritis, malignancy or renal failure that would prevent participation in fitness testing were excluded from the study.

Sample size calculations were carried out using the SAS power procedure for multiple linear regressions. The sample size was based on sufficient statistical power (0.8) to explain at least 40% of the variance with 20 predictor variables. Our calculations indicated that a sample of 143 participants would allow for *at least* 40% of the variation in the outcome to be detected. Because all 183 participants from the pilot study were included, this study had adequate statistical power to answer the question.

Procedure:

The ethics study was approved by the ethics committees of each of the hospitals and written informed consent was obtained from all participants.

The primary outcome measure was self-rated health status, measured using the EQ-5D Visual Analogue Scale (EQVAS). The predictor variables included both performance-based and self-reported measures of physical and cognitive capacity. Please refer to Table 8.1 for a complete list of the variables. In order to avoid or minimize fatigue, sufficient time between each performance test was given to participants.

Perceived health status. Perceived health status was measured using the EQ VAS. The EQVAS is embedded in the EQ-5D health-related quality of life questionnaire, which includes 5 separate domains; mobility, capacity for self-care, conduct of usual activities, pain/discomfort and anxiety/depression. The first part of the questionnaire was not used in this study. The second part of the questionnaire consists of a Visual Analogue Scale (VAS) to measure overall health status from the patient's perspective. Subjects were asked to rate their health condition on a vertical scale from 0 to 100, the former showing the worst imaginable health state, the latter marking the best imaginable health state. Good concurrent and discriminative validity has been demonstrated for the EQ-5D.[9, 10]

Aerobic capacity. The modified Canadian Aerobic Fitness Test (mCAFT), a multi-stage step test, was administered to assess aerobic capacity. Starting stage or stepping sequence was determined according to the patient's age. Subjects completed all the stages necessary to achieve 85% of their age predicted maximum heart rate. The final stage completed for each subject was recorded. Standardized instructions and procedures as outlined in the CPAFLA manual were used.[12]

Walking capacity. The 6MWT is a measure of functional walking capacity. Subjects were instructed to walk as far as possible in six minutes at their own pace. Standardized instructions and encouragements were used.[11]

Physical fitness. The push-ups, curl-ups, grip strength and jump test were administered to evaluate physical fitness. The push-ups and curl-ups assessed muscle endurance, whereas grip strength measured muscle strength. Lower limb power was evaluated through the vertical jump test. Tests were administered according to the Canadian Physical Activity Fitness and Lifestyle Appraisal (CPAFLA). Norm-referenced age and gender-specific averages are available for all of these tests.[12] Description of measures is provided in the previous article.

Cognitive function. Cognition was assessed with the Paced Auditory Serial Addition Test (PASAT) and the Perceived Deficits Questionnaire (PDQ). The PASAT is a direct measure of cognitive capacity that specifically assesses information processing speed, flexibility and attention.[14] It has been widely used in research and clinical practice for persons with MS. The assessment was carried out using a compact disk, where single digit numbers were presented every 3 seconds and subjects were instructed to add each coming new digit to the one immediately prior to it. The test is scored based on the total number of correct responses provided (maximum 60). This measure has moderate to high reliability and validity.[15-17]

The PDQ is patient-reported measure of perceived cognitive function designed for use in persons with MS. It contains 20 items that assess various domains of cognition: attention, memory, planning and organization.[18] Response options are in 5-point Likert scale, from “Never” to “almost always” and rates of “0” to “4” are given according to the response option selected. The total score is out of 80, where higher scores indicate greater cognitive impairment. Reliability and validity of the PDQ has been assessed in persons with MS.[19-21]

Disease severity. Disease severity was measured using the Expanded Disability Status Scale (EDSS). This is a widely used scale to measure level of disability in patients with MS. It is a classification scheme extending from 0 (normal neurological examination) to 10 (death due to MS).[13]

Domains of the SF-36. The Medical Outcomes Study Short Form-36 Health Survey (SF-36) is a health-related quality of life questionnaire that consists of 8 subscales as follows: physical functioning, role limitations due to physical problems (role-physical), bodily pain, general health perceptions, vitality, social functioning, role-limitations due to emotional problems (role-emotional), and mental health. Each subscale is scored on a scale of 0 to 100, with 100 representing the best possible health. For this study, all the sub-scales of the SF-36 except for general health perception and physical functioning were included in the model. General health perception was not included, for it evaluates the same construct as the outcome. And physical functioning was found to be collinear with one of the performance based measures, the six-minute walk test.

Socio-demographic variables. Age, sex, body mass index (BMI), education and smoking status were self-reported by patients and recorded on the day of testing.

Data Analysis

Basic descriptive statistics were employed to describe the characteristics of the sample. Patient's socio-demographic characteristics and scores on all measures were presented using means and standard deviations (SD). Pearson's correlation coefficients were calculated to evaluate the association of each predictor variable with the outcome.

The all-possible subset approach was used to identify the best predictor variables for the multiple linear regression model. The importance of each predictor variable was evaluated using statistical significance at the 0.05 level and by the drop in R-square, due to removal of the predictor variable from the model. Since the purpose of this study is to develop the best predictive model of perceived health status, all possible variables that have been found to be associated with the outcome were included in the model. The presence of significant interactions was checked out.

Regression diagnostics were used to verify that assumptions of multiple linear regression were not violated. Homoscedasticity and normality of residuals were assessed, and outliers identified.

All analysis was performed using the Statistical Analysis Systems (SAS) Version 9.1.

Results

A total of 183 participants underwent the performance-based testing to assess physical and mental capacity. The sample was young (mean age 43) and predominantly female. Both men and women had mild disability with a median EDSS score of 2. Demographic and clinical characteristics are presented in Table

8.2. For the fitness tests (push-ups, curl-ups, grip strength and jump test), each participants scores were compared to the age and gender specific Canadian norms. For the push-ups and the partial curl-ups, patients ranked at approximately 15th and 45th percentiles, respectively. Similar results were found for grip strength and the jump test, measures of upper and lower limb strength. The average distance ambulated during the 6MWT, a test of functional walking capacity, was 458 meters. By using an already developed multiple linear regression, each participant's results for the 6MWT were compared to pre-established age and sex specific reference values. Our sample performed at 66% of what normal healthy individuals with the same age, height, and weight would perform. Results are presented by gender in Figure 8.4. Scores on the SF-36 Health Survey were compared to Canadian norms, and as demonstrated by Figure 8.5, our sample had significantly lower scores on all of the domains.

The box plots of the outcome for men and women are presented in Figure 8.6. Women reported higher levels of perceived health status on the EQVAS than men-the women's mean score was 77%, the men's was 72%. The inter-quartile range for women was between 70% and 90%, whereas the men's was between 60% and 90%. As demonstrated by the box plots, there was greater variation in the EQVAS for men than for women.

The multiple linear regression analysis for the EQVAS included all performance-based measures and self-reported measures, as presented in Table 8.1. Age, sex, BMI, education, smoking status and disability level were also included in the model. When all of these variables were modeled together, sex, vitality, pain, smoking status, the 6MWT, social functioning and the PASAT emerged as significant predictors of the outcome ($p<0.05$). Aerobic capacity as measured by the mCAFT did not predict perceived health status. Significant interaction terms between sex and pain, as well as between sex and vitality were found. The association of pain and vitality with perceived health status was found to be greater for men than women. Due to our small sample size, the two interaction terms could not be presented in the same model at the same time. For each model, the variables are presented in order of size of the standardized coefficients, and each one was calculated by multiplying the standard deviation for the variable by its un-standardized parameter estimate. The standardized coefficient allowed us to standardize our variables and identify which variables had the largest effect on the outcome. For example, a 1 standard deviation increase in the 6MWT produced an average increase of 3 points on the EQVAS. In the models, vitality and pain were found to have the greatest impact on the outcome, whereas cognitive capacity and social functioning had the least effect. The PASAT, a measure of cognitive capacity, had a negative association with the EQVAS. This implies that individuals with higher cognitive capacity may be better aware of their health status, and therefore score themselves lower on the VAS. The multiple linear regression models explained 47% and 48% of the variance in the EQVAS. The standardized parameter estimates, un-standardized parameter estimates, and their p-values are presented in Table 8.3a and 8.3b.

As a result of the two significant interaction terms that emerged in the model, gender specific analyses were carried out, as well. Multiple linear regression analysis was performed for men and women separately. For women, vitality and role limitations due to physical problems and the PASAT surfaced as significant predictors explaining 37% of the variance in the EQVAS. For men, pain and the jump test, a measure of lower leg power, significantly predicted the outcome and described 55% of the variance. We were able to explain a greater proportion of the outcome for men because of the larger variance in the EQVAS. Although the effect of vitality on perceived health was found to be greater for men than for women, we were unable to detect this in the multiple linear regression model for men. This may be influenced by the large standard error in vitality for men. Variables such as the 6MWT and smoking status that appeared in the model with the whole sample were not identified in the gender specific models due to small sample size and inadequate power. Results are presented in Table 8.4a and 8.4b.

Discussion

The contributions to perceived health status appear to be different for men and women. A fair head-to-head comparison between sexes would require equal sample sizes; however, our sample was predominantly women. Our model was able to explain 50% of the variation in perceived health status. We were unable to explain more than this, probably due to small variance found in the EQVAS. Of course, we cannot eliminate the possibility that there may be unmeasured variables not included in the model. However, considering the wide range of predictor variables that were included, it is not easy, if not altogether impossible, to figure out what these unknown variables could be. But, one should perhaps admit the difficulty of explaining *all* of the variance in perceived health status.

An important strength of this study is that the sample was randomly selected from three different clinics in the greater Montreal area, from populations who were culturally diverse and who were residing in different urban/rural environments. The predictors of perceived health in persons with MS were assessed by Roberts and Stuifbergen in 1998.[23] However, an important methodological limitation was that their participants were solicited using membership rosters of MS societies; therefore, introducing possible volunteer or selection bias into their study. Furthermore, since there were no restrictions or stratifications according to date of diagnosis or disease onset, they only included survivors of the disease. We have restricted our sample to persons diagnosed after 1995 thereby eliminating the presence of survival bias.

A limitation of our study was the small sample size that did not allow us to detect more than one interaction term at a time. Furthermore, we were unable to conduct fair comparisons between men and women, due to unequal and insufficient sample sizes.

Identifying the predictors of perceived health status is important for both health professional and researchers, for perceived health status has repeatedly found to be a strong predictor of morbidity and mortality. Given the debilitating effects of

MS on the individual, it is important to determine the predictors of self-rated health. By determining the predictors of self-rated health, we can help improve patients' overall health status. Besides, knowledge about perceived health may provide targets for therapy and influence treatment approaches for people with MS.

TABLE 8.1 Classification and Measurement of Independent Variables in the Model

Predictor Variable	Measurement Scale	Units/Scoring/Coding
Performance-based		
Step test	Quasi-continuous	Stages
Push-ups	Ordinal	0 = 0 to 1 = 2 =
Curl-ups	Binary	0 = 0 to 15 curl-ups 1 = 16 to 25 curl-ups
Jump test	Continuous	Centimetres
Grip strength	Continuous	Kilograms
6MWT	Continuous	Meters
Paced Auditory Serial Addition Test (PASAT)	Continuous	Total number of answers correct
Expanded Disability Status Scale (EDSS)	Quasi-continuous	Score out of 10
Patient-reported		
SF-36: Role-physical	Continuous	Score out of 100
Bodily pain	Continuous	Score out of 100
Vitality	Continuous	Score out of 100
Social functioning	Continuous	Score out of 100
Role-emotional	Continuous	Score out of 100
Mental health	Continuous	Score out of 100
Perceived Deficits Questionnaire (PDQ)	Continuous	Score out of 80
Socio-demographic variables		
Age	Continuous	Years
Sex	Binary	0 = male 1 = female
Body Mass Index (BMI)	Continuous	kg/meters^2
Education	Binary	0 = high school or lower 1 = CEGEP or higher
Smoking Status	Binary	0 = non-smoker 1 = smoker

TABLE 8.2 Demographic and clinical characteristics of participants by gender

Characteristic	Women (n=135)	Men (n=48)
Age in years, mean (SD)	42.5 (9.7)	44.0 (11.6)
BMI in kg/m^2, mean (SD)	25.5 (6.2)	25.4 (4.6)
EDSS score†, median (IQR)	2.0 (1 to 4)	2 (1.5 to 6)
Current smoking status, No. (%)		
Yes	33 (24)	15 (31)
No	102 (76)	33 (69)
Education, No. (%)		
High School or below	36 (27)	8 (17)
CEGEP or above	99 (73)	40 (83)

SD, standard deviation; No., number; BMI, Body Mass Index;
EDSS, Expanded Disability Status Scale; IQR, Interquartile range
†Obtained from medical charts

FIGURE 8.4 Physical and cognitive test scores compared to Canadian norms

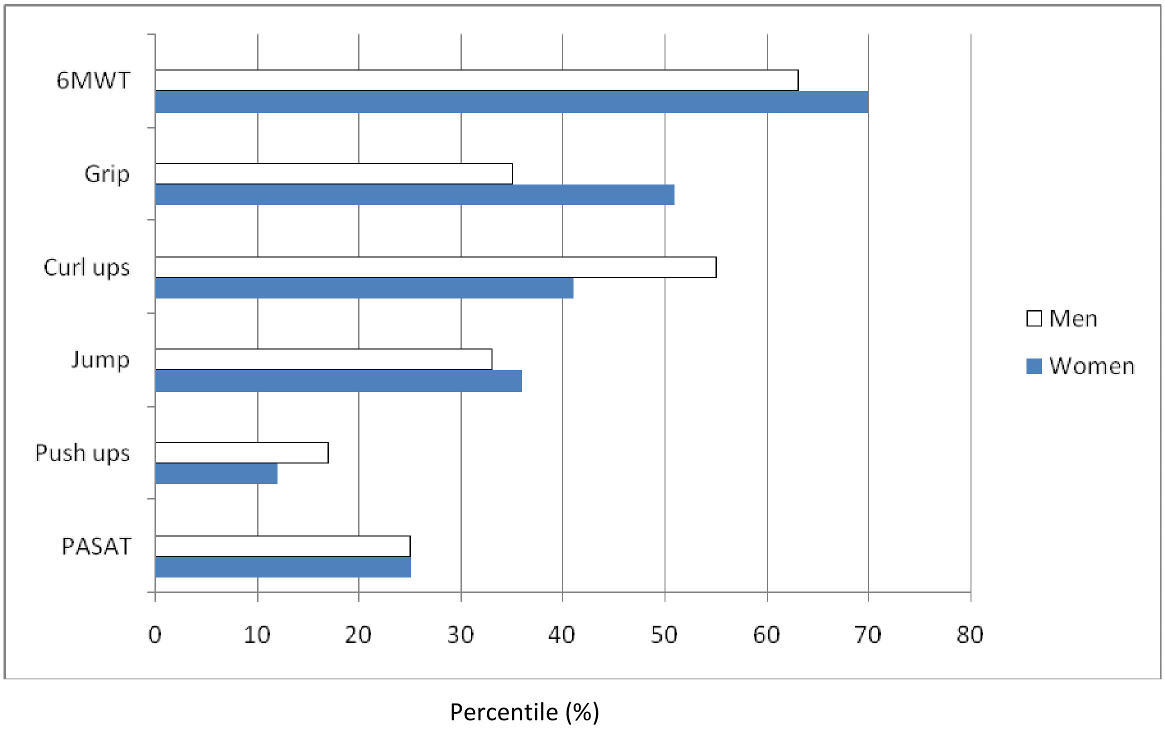

FIGURE 8.5 SF-36 profile for men and women compared to Canadian norms

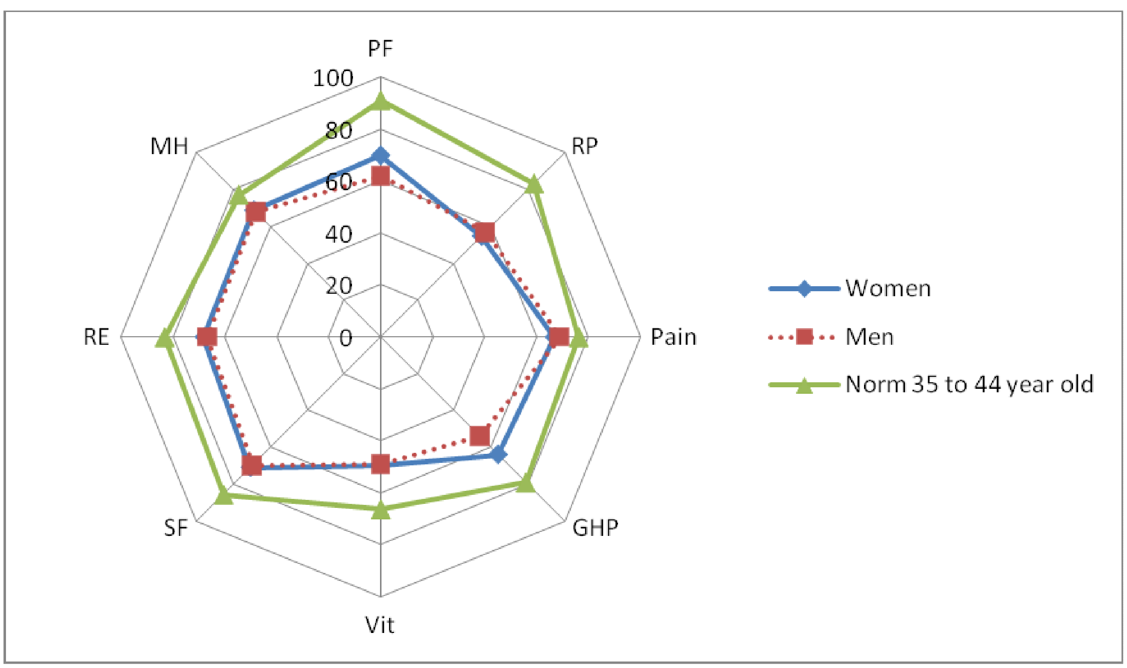

FIGURE 8.6 Box plots of the EQVAS for men and women

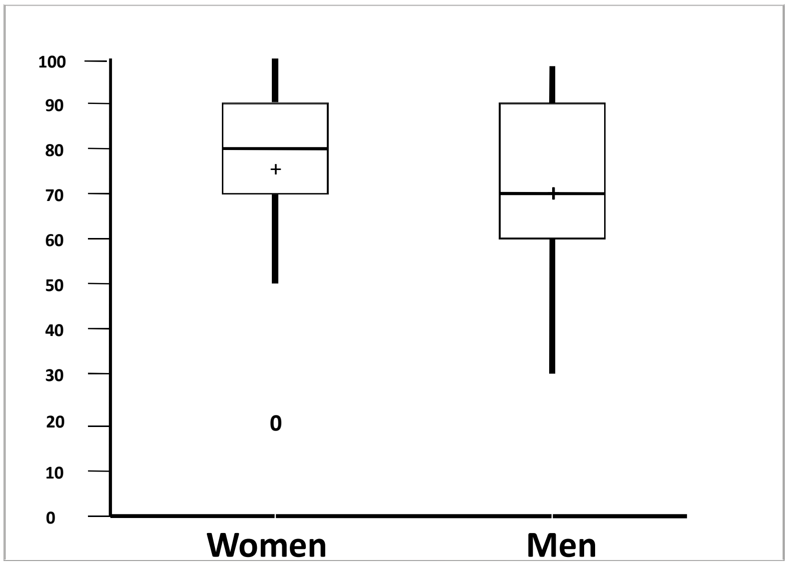

TABLE 8.3a Multiple linear regression model for perceived health status

	Unstandardized coefficients Beta	Standard Error	Standardized coefficients	P value
Sex (female)	17.9	6.10	17.9	0.02
Pain	0.29	0.08		0.0004
Sex*Pain	-0.18	0.08		0.008
Vitality	0.24	0.06	6.3	0.003
Current smoker	4.28	2.13	4.3	0.03
6MWT	0.02	0.006	3.4	0.01
Social functioning	0.11	0.05	2.6	0.04
PASAT	-0.20	0.08	-2.5	0.02

Outcome variable: EQ VAS. Total $R^2 = 0.48$, $p<0.0001$
Intercept is 32.2, standard error 5.9, $p<0.0001$
Standardized coefficient = βeta*SD of X

TABLE 8.3b Multiple linear regression model for perceived health status

	Unstandardized coefficients Beta	Standard Error	Standardized coefficients	P value
Sex (female)	14.6	5.54	14.6	0.007
Vitality	0.40	0.10		0.002
Sex*Vitality	-0.19	0.10		0.05
Current smoker	4.99	2.09	4.99	0.02
Pain	0.15	0.05	4.1	0.001
6MWT	0.02	0.006	3.4	0.004
Social functioning	0.11	0.05	2.6	0.027
PASAT	-0.23	0.08	-2.5	0.007

Outcome variable: EQ VAS. Total $R^2 = 0.47$ $p<0.0001$
Intercept is 35.2, standard error 5.4, $p<0.0001$
Standardized coefficient = βeta*SD of X

TABLE 8.4a Multiple linear regression model for perceived health status in women

	Unstandardized coefficients Beta	Unstandardized coefficients Standard Error	Standardized coefficients	P value
Vitality	0.29	0.06	6.09	<0.0001
Role-Physical	0.11	0.03	4.73	0.0002
PASAT	-0.17	0.08	-2.38	0.046

Total R^2 = 0.37, p<0.0001
Intercept is 64.3, standard error 4.0, p<0.0001
Standardized coefficient = βeta*SD of X

TABLE 8.4b Multiple linear regression model for perceived health status in men

	Unstandardized coefficients Beta	Unstandardized coefficients Standard Error	Standardized coefficients	P-value
Pain	0.45	0.09	12.2	<0.0001
Jump test	0.40	0.12	5.2	0.002

Total R^2 = 0.55, p<0.0001
Intercept is 31.6, standard error 6.1, p<0.0001
Standardized coefficient = βeta*SD of X

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CHAPTER 9

Conclusion

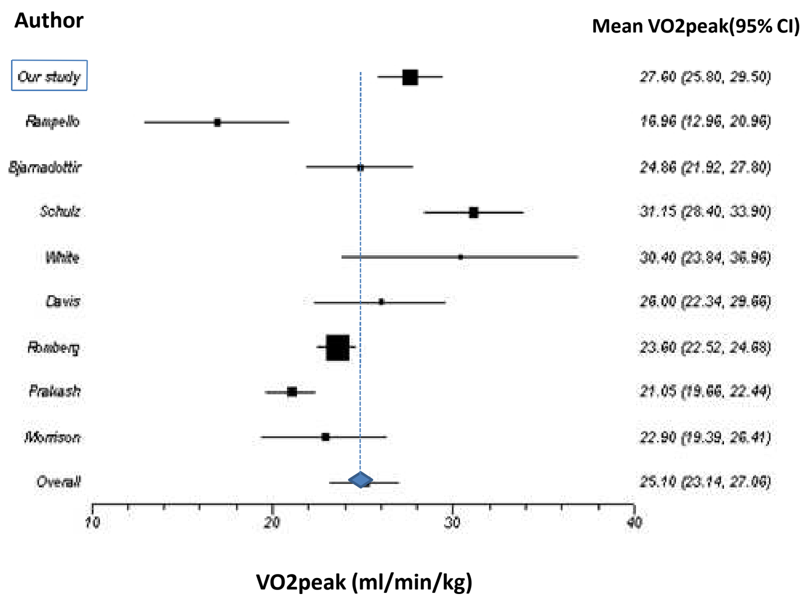
Multiple sclerosis (MS) is a chronic disease with an unpredictable course that impacts significantly on all aspects of patients' lives. It is not only important to understand the impact of the disease on exercise capacity through objective measures, but also to observe its impact from the patient's perspective. This thesis has targeted both of these objectives in this disease population. From our findings we are able to draw several important conclusions on the disease process and overall health status of persons with MS.

In the first manuscript, we assessed the impact of MS on exercise capacity. Exercise or fitness has become an essential part of management and health promotion in this group. The gold standard measure of exercise capacity is the maximal exercise test which is accepted as the best measure of cardio-respiratory capacity or fitness. Besides being very demanding and requiring specialized equipment, this test has no application for self-management, as people with MS who attempt to be more actively engaged in taking charge of their fitness level and to improve their exercise capacity cannot self-monitor with this test. Therefore, using a series of sub-maximal tests, we are able to formulate a regression equation whereby the mCAFT, grip strength, and body weight emerged as significant predictors, explaining 74% of the variance in peak aerobic capacity (VO_{2peak}).

In addition, we have compared our samples VO_{2peak} to the MS literature in order to understand how our sample looked like as compared to other studies. We have redrawn our forest-plot from Chapter 3, but this time adding our study's findings to it. As displayed in Figure 9.1, our study had a relatively large sample size and narrow confidence interval in comparison to the other studies. The VO_{2peak} values of our participants are similar to the findings of the other studies with a mean of 27ml/kg/min and a 95% confidence interval between 25.8 and 29.5 ml/kg/min. Our study confirms that exercise capacity is markedly reduced in persons with MS even with mild disability levels. These findings have important implications for clinical practice, as it emphasizes the strong need for health promotion and education in persons with MS. Of course, we cannot exclude the possibility that such low levels of exercise capacity may not only be due to physical inactivity, but also because of the disease process itself. However, impairments associated with the disease can still lead to a gradual deterioration of functioning in daily life; hence, exercise remains a major strategy in maintaining and improving functional status.

The second part of this thesis has evaluated the impact of the disease from the patients' perspective. Understanding patients' own perceptions of the impact of symptoms on their overall health status and their well-being has important clinical implications, as it can influence treatment approaches in persons with MS. Perceived health status is easy to measure and can also provide useful information concerning a person's well-being and overall HRQL. It is a strong predictor of mortality, morbidity and disease progression; therefore, understanding the predictors of perceived health status itself can provide targets or directions for rehabilitation. Our results indicated that sex, vitality, pain, smoking status, walking capacity, social functioning and cognitive capacity explained approximately 50% of the variance in perceived health status. Significant interaction terms between sex and pain, as well as between sex and vitality have been noticed. Our findings have demonstrated that the contributions to perceived health status are different for men and women, where the association between pain and vitality with perceived health status is greater for men than is for women.

Figure 9.1 Forest plot of our sample's VO_{2peak} in comparison to MS literature



*Standard deviation for the study by Bjarnadottir et al. is estimated from the other studies.

*Standard deviation for the overall mean is assumed from the study by Romberg as it has the largest sample size.

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APPENDICES

A1.0 Description of Measures

A) Grip strength
B) The Modified Canadian Aerobic Fitness Test (mCAFT)
C) Push-ups
D) Partial Curl-ups
E) Vertical Jump Test
F) The Six-Minute Walk Test (6MWT)
G) Expanded Disability Status Scale (EDSS)
H) Equi-Scale
I) Modified Ashworth Scale (MAS)
J) EQ-5D Visual Analogue Scale of Health Status
K) Paced Auditory Serial Addition Test (PASAT)
L) Perceived Deficits Questionnaire (PDQ)
M) SF-36 Health Status Survey

A) Grip Strength (Instructions/Report sheet)

Subjects are seated on a standard height chair without armrests with their elbow at 90 degrees. Three grip strength measures of each hand are taken using the Jamar dynamometer. The sum of the highest scores for the right and left hand will be retained.

Right hand:	1) __________	Left hand:	1) __________
	2) __________		2) __________
	3) __________		3) __________

B) The Modified Canadian Aerobic Fitness Test (mCAFT)

1. Measure resting heart rate.
2. Explain the purpose of the test and how it is conducted.
3. Determine the starting stage for clients, based on their age, according to the table below.

	Starting Stage by Age and Gender	
Age	Males	Females
60-69	1	1
50-59	2	1
40-49	3	2
30-39	3	3
20-29	4	3
15-19	4	3

4. Determine the cadence (footplants/min) depending on the stage assigned.

	Cadence (footplants/min)	
Stage	**Males**	**Females**
1	**66**	**66**
2	**84**	**84**
3	**102**	**102**
4	**114**	**114**
5	**132**	**120**
6	**144**	**132**
7	**118**	**144**
8	**132**	**118**

**Stages 1 to 6 are use a two-step pattern on the double 20.3cm steps. Stages 7 & 8 use a single- step pattern on a step 40.6cm in height.*

5. Demonstrate the stepping exercise sequence as follows for stages 1 to 6:
   i. Place your right foot on the first step
   ii. Place your left foot on the second step
   iii. Place your right foot on the second step so feet are together
   iv. Start down with your left foot to the first step
   v. Place your right foot on the ground level
   vi. Place your left foot down on ground level so feet are together.

   For stages 7 & 8 the instructions are as follows:
   i. Place your right foot on the step
   ii. Place your left foot on the step s feet are together
   iii. Place your right foot on ground level,
   iv. Place your left foot down on ground level so feet are together.

**Note: Subjects may start stepping with either foot. The examples above begin with the right.*

6. The subject now practices the stepping sequence, first without the music and then with it, but not more than twice each time. Clients must *step* up and down, not run,
7. Ensure proper cadence is maintained. Count and/or step a few steps with anyone experiencing difficulty.
8. Start the CD. (Instructions and time signals are given on the CD as to when to start and stop exercising).
9. Person starts the stepping session.
10. When the music stops, subject stops stepping and remains motionless.
11. Evaluator immediately records heart rate for 10 seconds.
12. If the predetermined ceiling post-exercise heart rate is not attained or exceeded, the subject goes on to the next level. Refer to the below for ceiling post-exercise heart rates.

	Heart rate*			**Heart rate***	
Age	**10sec count**	**Monitor reading**	**Age**	**10sec count**	**Monitor reading**
15	29	174	43	25	150
16	28	173	44	25	150
17	28	173	45	25	149
18	28	172	46	24	148
19	28	171	47	24	147
20	28	170	48	24	146
21	28	169	49	24	145
22	28	168	50	24	145
23	28	167	51	24	144
24	28	167	52	24	143
25	27	166	53	23	142
26	27	165	54	23	141
27	27	164	55	23	140
28	27	163	56	23	139
29	27	162	57	23	139
30	27	162	58	23	138
31	27	161	59	23	137
32	26	160	60	22	136
33	26	159	61	22	135
34	26	158	62	22	134
35	26	157	63	22	133
36	26	156	64	22	133
37	26	156	65	22	132
38	26	155	66	22	131
39	25	154	67	21	130
40	25	153	68	21	129
41	25	152	69	21	128
42	25	151			

(The Canadian Physical Activity, Fitness & Lifestyle Appraisal, 3rd edition, 2004)

C) Push-Ups (instructions/procedure)

Men:

1. The subject lies on his stomach, legs together, hands pointing forward positioned under the shoulders.
2. He then pushes up by fully straightening the elbows and using the toes as the pivot point. The upper body must be kept in a straight line.
3. The subject returns to starting position, but neither the stomach nor thighs should touch the mat.
4. Subjects should practice one or two repetitions to check for proper technique before starting test.
5. Push-ups are performed consecutively and without a time limit.
6. Test is stopped when subjects are seen to strain forcibly or are unable to maintain the proper push-up technique over two consecutive repetitions.

Women:

1. The subject lies on his stomach, legs together, hands pointing forward positioned under the shoulders.
2. She then pushes up by fully straightening the elbows and using the knees as the pivot point. The upper body must be kept in a straight line.
3. Subject returns to starting position. The stomach should not touch the mat, ankles are plantar-flexed (extended), and feet are in contact with the mat.
4. Subjects should practice one or two repetitions to check for proper technique before starting test.
5. Push-ups are performed consecutively and without a time limit.
6. Test is stopped when subjects are seen to strain forcibly or are unable to maintain the proper push-up technique over two consecutive repetitions.

(The Canadian Physical Activity, Fitness & Lifestyle Appraisal, 3rd edition, 2004)

D) Partial Curl-Up

1. Subjects lie supine with the knees flexed to 90^o. Heels are in contact with the mat.
2. A metronome can be used to provide a cadence of 25 beats per minute.
3. The subject performs slow curling up of the upper spine so that the middle finger reaches the mark made by the therapist prior to testing (See CPAFLA manual for details)
4. The number of consecutive curl-ups completed for 1 minute is recorded. Maximum number of curl-ups is 25.
5. Test is stopped if the subject: experiences undue discomfort, is unable to maintain required cadence or proper curl-up technique.

(The Canadian Physical Activity, fitness & Lifestyle Appraisal, 3rd edition, 2004)

E) Vertical Jump

1. A measuring tape is attached to the wall.
2. Subject stands facing sideways to the wall, feet flat on the ground, with the arm and fingers fully extended, and palm facing the wall.
3. Record the height.
4. Subject moves slightly away from the wall.
5. The arms are brought downward and backward while bending the knees in a semi-squat position.
6. Individual jumps as high a possible with the arms moving forward and backward, touching the tape at the peak height of the jump.
7. Subtract initial height from peak height. Round answer to the nearest 0.5cm.
8. Perform two more trials.
9. Using the highest jump from three trials, calculate leg power using the following equations:

$$\text{Average Power (Watts)} = \sqrt{4.9} \cdot \text{body mass (kg)} \cdot \sqrt{\text{jump-reach score (m)}} \cdot 9.81$$

$$\text{Peak Anaerobic Power (Watts)} = 60.7 \cdot \text{jump height(cm)} + 45.3 \cdot \text{body mass(kg)} - 2055$$

(The Canadian Physical Activity, Fitness & Lifestyle Appraisal, 3rd edition, 2004)

F) The Six-Minute Walk Test (6MWT)

1. Record patient's baseline heart rate using a heart rate monitor and level of fatigue using the Visual Analogue Scale. Use the Borg Scale of Perceived Exertion to measure level of effort.
2. Say to the patient:

   "The object of this test is to walk back and forth as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting but must resume walking as soon as you are able. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog."

   The pace will be determined by the patient. The physiotherapist should walk slightly behind the patient so as not to pace them.

3. Encouragement must be standardized as it has been shown to increase walking speed. Standardized encouragement was given to all subjects every 30 seconds. The subjects were told:*

   "You're doing well, keep up the good work".

4. Perceived level of exertion is measured on the Borg scale and fatigue is measured using the Visual Analogue Scale pre and post-testing. Total distance walked and the number and duration of rest periods required are noted.

G) Expanded Disability status Scale (EDSS)

0.0 - Normal Neurological Exam
1.0 - No disability, minimal signs on 1 functional systems (FS)
1.5 - No disability minimal signs on 2 of 7 FS
2.0 - Minimal disability in 1 of 7 FS
2.5 - Minimal disability in 2 FS
3.0 - Moderate disability in 1 FS; or mild disability in 3 - 4 FS, though fully ambulatory
3.5 - Fully ambulatory but with moderate disability in 1 FS and mild disability in 1 or 2 FS; or moderate disability in 2 FS; or mild disability in 5 FS
4.0 - Fully ambulatory without aid, up and about 12hrs a day despite relatively severe disability. Able to walk without aid 500 meters
4.5 - Fully ambulatory without aid, up and about much of day, able to work a full day, may otherwise have some limitations of full activity or require minimal assistance. Relatively severe disability. Able to walk without aid 300 meters
5.0 - Ambulatory without aid for about 200 meters. Disability impairs full daily activities
5.5 - Ambulatory for 100 meters, disability precludes full daily activities
6.0 - Intermittent or unilateral constant assistance (cane, crutch or brace) required to walk 100 meters with or without resting
6.5 - Constant bilateral support (cane, crutch or braces) required to walk 20 meters without resting
7.0 - Unable to walk beyond 5 meters even with aid, essentially restricted to wheelchair, wheels self,
transfers alone; active in wheelchair about 12 hours a day
7.5 - Unable to take more than a few steps, restricted to wheelchair, may need aid to transfer; wheels self, but may require motorized chair for full day's activities
8.0 - Essentially restricted to bed, chair, or wheelchair, but may be out of bed much of day; retains self care functions, generally effective use of arms
8.5 - Essentially restricted to bed much of day, some effective use of arms, retains some self care functions
9.0 - Helpless bed patient, can communicate and eat
9.5 - Unable to communicate effectively or eat/swallow
10.0 – Death

(Kurtzke, 1983)

H) Equi-Scale

Easiest

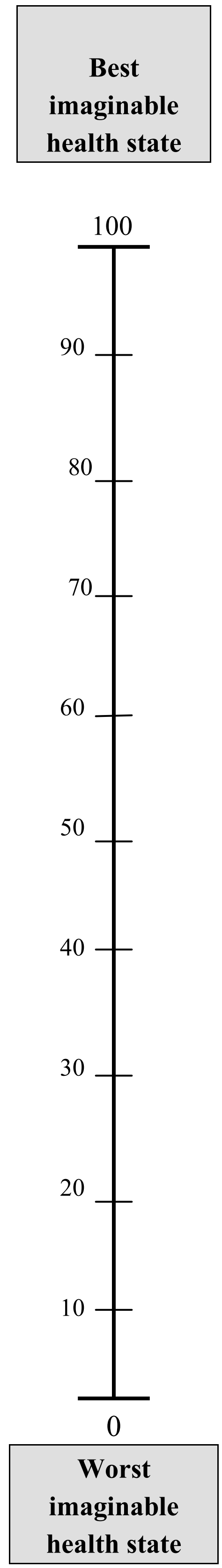
Task	Directions/Procedures	Description	Score
1. Sitting balance	Sitting with back unsupported but feet supported on floor or on a stool	Unable to sit without support 10 seconds Able to sit 10 - 30 seconds Able to sit safely and securely 2 minutes	= 0 = 1 = 2
2. Standing balance	Standing still	Unsteady Steady but wide stance (medial heels > 4 inches apart) and uses cane or other support Narrow stance without support	= 0 = 1 = 2
3. Sit-to-stand	Use a conventional chair	Needs help or unable Uses arms to push him/herself Succeeds alone, without arms	= 0 = 1 = 2
4. Nudge	Stand with feet as close together as possible, eyes open. Examiner pushes lightly on subject's sternum with palm of hand three times in about 15 seconds, at pseudo-random intervals. The subject resists nudges.	Fall or step, all three times Fall or step, 1 or 2 out of 3 times Stable 3 times	= 0 = 1 = 2
5. Lean forward	Stand with feet together; eyes open; raise the arms to horizontal position; lean forward about 25 cm, making the hand follow, parallel, a piece of paper held by the examiner	Leans for less than 10 cm 10-24cm 25 cm or more	= 0 = 1 = 2
6. Pick-up	Stand with feet together. Pick up a pen placed on the floor, 20cm in front of toes. Go back to standing.	Unable to complete One partial attempt, then full task completed	= 0 = 1

		Full task completed at first attempt	= 2
7. Stand with eyes closed	Eyes closed feet together; arms folded on the chest.	Stands less than 5s 5 to 19s 20s or more	= 0 = 1 = 2
8.Rotate	Stand eyes open, free distance between feet. Turn around “quickly” on the spot. After about 5 seconds, repeat in opposite direction.	Completely unable to perform the task Able to rotate in one direction in 4s or more, not in both directions in less than 4s each Both rotations completed in less than 4s each	= 0 = 1 = 2
9. Stand with eyes closed, head extended	Eyes closed feet together; arms folded on the chest; extend the head maximally; wait 5s before timing	Stands less than 10s 10-29s 30s or more	= 0 = 1 = 2
Hardest 10. Tandem stance	Position the left foot, displaced leftwards about 3cm, in front of the right foot. Orient both feet sagittally. The front heel must touch rear toes. Support can be provided for a few seconds before timing starts. Repeat with left foot behind.	Fall or step before 5s in both positions Stands at least 5s in one position, not for 15s in both At least 15s in both positions	= 0 = 1 = 2
		Total score (maximum = 20):	

I) EQ-5D Visual Analogue Scale of Health Status

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked by 100 and the worst state you can imagine is marked by 0.

We would like you to indicate on this scale how good or bad is your own health **<u>today</u>**, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your current health state is.



Your own health state today

J) Paced Auditory Serial Addition Test (PASAT)

PRACTICE	9+1 10__	3 4__	5 8__	2 7__	6 8__	4 10__	9 13__	7 16__	1 8__	4 5__

Total Score_____

Percent Correct____

1+4 5__	8 12__	1 9__	5 6__	1 6__	3 4__	7 10__	2 9__	6 8__	9 15__
4 13__	7 11__	3 10__	5 8__	3 8__	6 9__	8 14__	2 10__	5 7__	1 6__
5 6__	4 9__	6 10__	3 9__	8 11__	1 9__	7 8__	4 11__	9 13__	3 12__
7 10__	2 9__	6 8__	9 15__	5 14__	2 7__	4 6__	8 12__	3 11__	1 4__
8 9__	5 13__	7 12__	1 8__	8 9__	2 10__	4 6__	9 13__	7 16__	9 16__
3 12__	1 4__	5 6__	7 12__	4 11__	8 12__	1 9__	3 4__	8 11__	2 10__

Instructions:

"On this tape (or CD) you are going to hear a series of single digit numbers that will be presented at the rate of one every 3 seconds. Listen for the first two numbers, add them up, and tell me your answer. When you hear the next number, add it to the one you heard on the tape right before it. Continue to add the next number to each preceding one. Remember, you are not being asked to give me a running total, but rather the sum of the last two numbers that were spoken on the tape (or CD)."

Write the numbers 5, 7, 3, and 2 from left to right on a sheet of paper. Then give the following instruction: ***"For example, if the first two numbers are '5' and '7,' you would say '12.' If the next number is '3' you would say _____"*** (pause for an answer from patient). If the patient gives a running total (i.e., "15") or a number other than "10," provide the correct number and explain the task again before going on. ***"Then if the next number is '2' you would say _____"*** (pause for an answer from patient). If the patient fails to say "5," provide the answer and proceed to the practice items.

Then say, **"This is a challenging task. If you lose your place, just jump right back in listen for two numbers in a row and add them up and keep going. There are some practice items at the beginning of the tape (or CD). Let's try these first."**

Administer the practice sequence a maximum of three times. Record answers in the space provided on the PASAT Practice Form. If the patient gets at least 2 answers correct (consecutive or not) on any of the practice sequences proceed to administer the 3" PASAT test. Once it is clear that the patient possesses sufficient understanding of the task, begin PASAT 3” test.

(Multiple Sclerosis Composite Function Scale MFSC)

K) Perceived Deficits Questionnaire (PDQ)

The following questions describe several situations in which a person may encounter problems with memory, attention or concentration. If you are marking your own answers, please check the appropriate response based on your cognitive function during the <u>past 4 weeks.</u> <u>Please answer every question.</u> If you are not sure which answer to select, please choose the one answer that comes closest to describing you.

During the **<u>past 4 weeks</u>**, how often did you....

1. Lose your train of thought when speaking?

Never	Rarely	Sometimes	Often	Almost always
❑	❑	❑	❑	❑

2. Have difficulty remembering the names of people, even ones you have met several times?

Never	Rarely	Sometimes	Often	Almost always
❑	❑	❑	❑	❑

3. Forget what you came into the room for?

Never	Rarely	Sometimes	Often	Almost always
❑	❑	❑	❑	❑

4. Have trouble getting things organized?

Never	Rarely	Sometimes	Often	Almost always
❑	❑	❑	❑	❑

5. Have trouble concentrating on what people are saying during a conversation?

Never	Rarely	Sometimes	Often	Almost always
❑	❑	❑	❑	❑

6. Forget if you had already done something?

Never	Rarely	Sometimes	Often	Almost always
❑	❑	❑	❑	❑

7. Miss appointments and meetings you had scheduled?

Never	Rarely	Sometimes	Often	Almost always
❑	❑	❑	❑	❑

8. Have difficulty planning what to do in the day?

Never	Rarely	Sometimes	Often	Almost always
❑	❑	❑	❑	❑

9. Have trouble concentrating on things like watching a television program or reading a book?

Never	Rarely	Sometimes	Often	Almost always
❑	❑	❑	❑	❑

10. Forget what you did the night before?

Never	Rarely	Sometimes	Often	Almost always
❑	❑	❑	❑	❑

11. Forget the date unless you looked it up?

Never	Rarely	Sometimes	Often	Almost always
❑	❑	❑	❑	❑

12. Have trouble getting started, even if you had a lot of things to do?

Never	Rarely	Sometimes	Often	Almost always
❑	❑	❑	❑	❑

13. Find your mind drifting?

Never	Rarely	Sometimes	Often	Almost always
❑	❑	❑	❑	❑

14. Forget what you talked about after a telephone conversation?

Never	Rarely	Sometimes	Often	Almost always
❑	❑	❑	❑	❑

15. Forget to do things like turn off the stove or turn on your alarm clock?

Never	Rarely	Sometimes	Often	Almost always
❑	❑	❑	❑	❑

16. Feel like your mind went totally blank?

Never	Rarely	Sometimes	Often	Almost always
❑	❑	❑	❑	❑

17. Have trouble holding phone numbers in your head, even for a few seconds?

Never	Rarely	Sometimes	Often	Almost always
❑	❑	❑	❑	❑

18. Forget what you did last weekend?

Never	Rarely	Sometimes	Often	Almost always
❑	❑	❑	❑	❑

19. Forget to take your medication?

Never	Rarely	Sometimes	Often	Almost always
❑	❑	❑	❑	❑

20. Have trouble making decisions?

Never	Rarely	Sometimes	Often	Almost always
❑	❑	❑	❑	❑

L) SF-36 Health Status Survey

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is:

(Circle one)

Excellent	1
Very good	2
Good.	3
Fair	4
Poor	5

2. <u>Compared to one year ago</u>, how would you rate your health in general now?

(Circle one)

Much better now than one year ago.	1
Somewhat better now than one year ago	2
About the same as one year ago	3
Somewhat worse now than one year ago	4
Much worse now than one year ago	5

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(Circle one number on each line)

	Yes, Limited A Lot	**Yes, Limited A Little**	**No, Not Limited At All**
a. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports.	1	2	3
b. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing **several** flights of stairs	1	2	3
e. Climbing **one** flight of stairs	1	2	3
f. Bending, kneeling, or stooping	1	2	3
g. Walking **more than a kilometre**	1	2	3
h. Walking **several blocks**	1	2	3
i. Walking **one block**	1	2	3
j. Bathing or dressing yourself	1	2	3

4. During the past 4 weeks have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

(Circle one number on each line)

	YES	**NO**
a. Cut down the **amount of time** you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Were limited in the **kind** of work or other activities	1	2
d. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(Circle one number on each line)

	YES	***NO***
a. Cut down the **amount of time** you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Didn't do work or other activities as **carefully** as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

(Circle one)

Not at all 1
Slightly 2
Moderately 3
Quite a bit 4
Extremely 5

7. How much bodily pain have you had during the past 4 weeks?

(Circle one)

None 1
Very mild 2
Mild 3
Moderate 4
Severe 5
Very severe 6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

(Circle one)

Not at all	1
A little bit	2
Moderately	3
Quite a bit	4
Extremely	5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks

(Circle one number on each line)

	All of the Time	**Most of the Time**	**A Good Bit of the Time**	**Some of the Time**	**A Little of the Time**	**None of the Time**
a. Did you feel full of pep?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6
f. Have you felt downhearted and blue?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

(Circle one)

All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

11. How **TRUE** or **FALSE** is each of the following statements for you?

(Circle one number on each line)

	Definitely True	**Mostly True**	**Don't Know**	**Mostly False**	**Definitely False**
a. I seem to get sick a little easier than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5

A2.0

Sample size calculation for manuscript #1

Prior to carrying out the study, sample size was estimated using the SAS power procedure for multiple linear regression. For this study we have used the data previously obtained by Mayo and colleagues on maximal exercise testing in persons with colorectal cancer. They found that age and sex alone explained 50% of the variance in VO_{2peak}. With our sub-maximal tests included in the model, we would easily be able to explain an additional 15% of the variance. Therefore, the sample size for this study was based on having sufficient statistical power (0.8) to explain at least 64% of the variance with 10 predictor variables and 4 confounding variables. Calculations indicated that a sample size of 58 subjects would be required to detect at least 64% of the variation in VO_{2peak}.

Sample size calculation for manuscript #2

The sample size was calculated using the SAS power procedure for multiple linear regression.The sample size was based on sufficient statistical power (0.8) to explain at least 40% of the variance with 20 predictor variables. Our calculations indicated that a sample of 143 participants would allow for *at least* 40% of the variation in the outcome to be detected.

A 3.0 Literature review for VO_{2peak} in MS

Authors, Year, Country	Sample size	Gender (M/F)	Mean age (yr) ± SD	Mean EDSS ± SD	Type of ergometer	Mean VO_{2peak} (ml/kg/min) ± SD
White et al. 2000 USA	6	3/3	46 ± 7	3.1 ± 0.9	Arm-leg	30.4 ± 8.2
Romberg et al. 2004 Finland	95	34/61	Male: 44.4 ± 6.8 Female: 43.5 ± 6.6	Male: 3.0 ± 1.2 Female: 2.2 ± 0.9	Cycle	Male: 27.0 ± 5.2 Female: 21.7 ± 5.5
Schulz et al. 2004 Germany	Training: 15 Control: 13	Training: 4/11 Control: 5/8	Training: 39 ± 9 Control: 40±11	Training: 2.0 ± 1.4 Control: 4.0 ± 0.8	Cycle	Training: 33.1 ± 7.1 Control: 28.9 ± 7.8
Davis et al. 2004 USA	10	0/10	44.7 ± 8.0	5.2 ± 1.3	Arm-leg	26.0 ±5.9
Prakash et al. 2006 USA	24	0/24	44.71±7.07	2.61 ± 1.76	Cycle	High fit group: 25.41 ± 4.82 Low-fit group: 16.68 ± 2.13
Rampello et al. 2007 Italy	11	3/8	44±6	Median: 3.5 Range: 1–4	Cycle	Group A: 16.8 ± 6.5 Group B: 17.1 ± 7.0
Bjarnadottir et al. 2007 Iceland	Group A: 6 Group B: 10	Group A: 3/3 Group B: 2/8	Group A: 38.7 Group B: 36.1	Group A: 2.1 Group B: 1.8	Cycle	Group A: 27.3 Group B: 23.4
Morrison et al. 2008 USA	12	Not given	38.3 ± 4.9	2.75 range: 0 –3	Cycle	22.9 ± 6.2